BENAVIDES, AMANDA RAHE, M.S. Facile Synthesis of Enantioenriched Hydroxy Esters via A Brønsted Acid Catalyzed Kinetic Resolution (2014) Directed by Dr. Kimberly Petersen. 107 pp.

The synthesis of natural products is a growing area of research within the field of chemistry. Compounds are extracted from sources such as fungi, plants, algae, and other natural sources. The compounds that are biologically active often need to be synthesized in the laboratory due to the fact that the natural resources only contain scant amounts of the active compound.

In this research, kinetic resolution, a form of asymmetric synthesis, is used in conjunction with Brønsted acid catalysts to form enantioenriched small molecules that can later be used in the synthesis of natural products. The Petersen lab chose to focus on substituted γ-hydroxy *tert*-butyl esters. The small molecule was lactonized via a Brønsted acid catalyzed kinetic resolution yielding enantioenriched starting material. In kinetic resolution, the maximum amount of material that can be achieved is 50% with an enantiomeric excess of 100%.

Initial optimization was conducted on α-substituted γ-hydroxy *tert*-butyl esters which showed that R-TRIP was the best catalyst in the kinetic resolution. γ-Substituted and disubstituted γ-hydroxy *tert*-butyl esters were tested with the *syn*-α,γ-dimethyl substrate showing the highest selectivity (s = 15.6). Cyclic hydroxy esters are currently being tested.

FACILE SYNTHESIS OF ENANTIOENRICHED HYDROXY ESTERS VIA A BRØNSTED ACID CATALYZED KINETIC RESOLUTION

by

Amanda Rahe Benavides

A Thesis Submitted to
the Faculty of the Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Greensboro
2014

Approved by

_____
Committee Chair

To my family and friends,
to Genesis and Momma

APPROVAL PAGE

This thesis has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina Greensboro

Committee Chair_____

Committee Members_____

_____

_____

_____
Date of Acceptance by Committee

_____
Date of Final Oral Examination

TABLE OF CONTENTS

LIST OF TABLES

Page

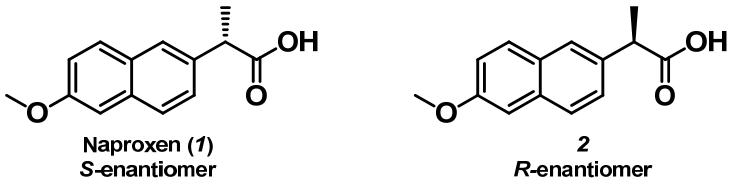
LIST OF FIGURES

Page

CHAPTER I

BACKGROUND AND SIGNIFICANCE

Asymmetric syntheses have gained interest over the last few decades as pharmaceutical companies begin the switch to nonracemic medications. This is due in part to the extended patent life that companies can obtain by separating enantiomers of an already known racemic compound; but many drugs will have one active stereoisomer and while the other is inactive or harmful. In the case of 2-(6-methoxynaphthalen-2-yl)propanoic acid (figure **1**), the *S*-enantiomer is known as Naproxen (**1**), a medication used to relieve pain, fever, and inflammation brought on by arthritis.



Naproxen (*1*)
S-enantiomer

2
R-enantiomer

Figure 1. The *R*- and *S*-Enantiomers of Naproxen

The *R*-enantiomer (**2**) is much less potent than the *S*-enantiomer.[1] The purpose of an asymmetric synthesis is to prepare stereochemically-enriched compounds efficiently. This chapter will touch on three key points of asymmetric synthesis: kinetic resolution, chiral Brønsted acid catalysts, and small-molecule synthesis.

1.1 Kinetic Resolution

Asymmetric syntheses[2] fall into three broad categories; chiral pool, enantioselective synthesis, and resolution. A chiral pool asymmetric synthesis is one in which the starting material is an enantiopure natural product. In the synthesis developed by Yan and group[3] (figure **2**), commercially available *L*-tartaric acid (**3**) served as the chiral pool to yield unnatural pinitols, shikimic acids, and their analogues.

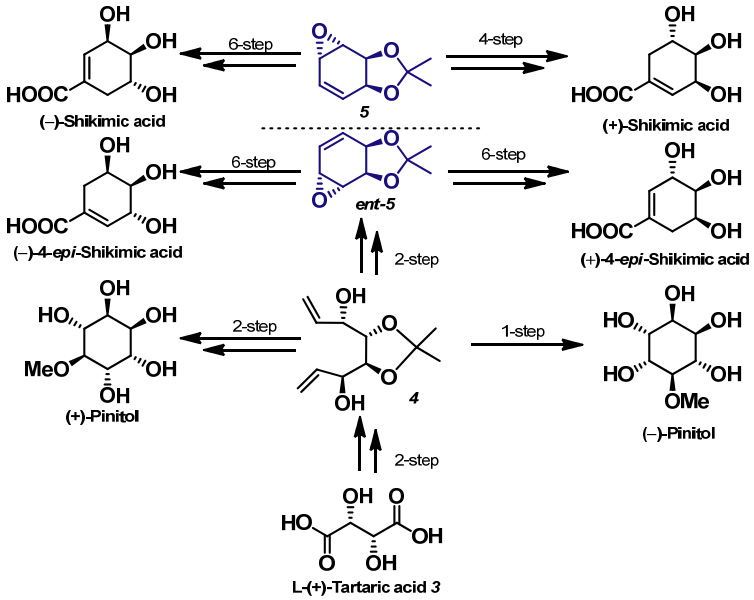


Figure 2. Retrosynthesis of Pinitol and Shikimic Acid via L-Tartaric Acid

An enantioselective synthesis uses achiral precursors and the reaction of these compounds with chiral reagents or catalysts. In the synthesis developed by Trost and Miege[4], *syn* β-hydroxy α-amino esters can be formed enantioselectively through the asymmetric aldol reaction of glycine Schiff bases and aldehydes using a zinc-ProPhenol-catalyst (**8**).

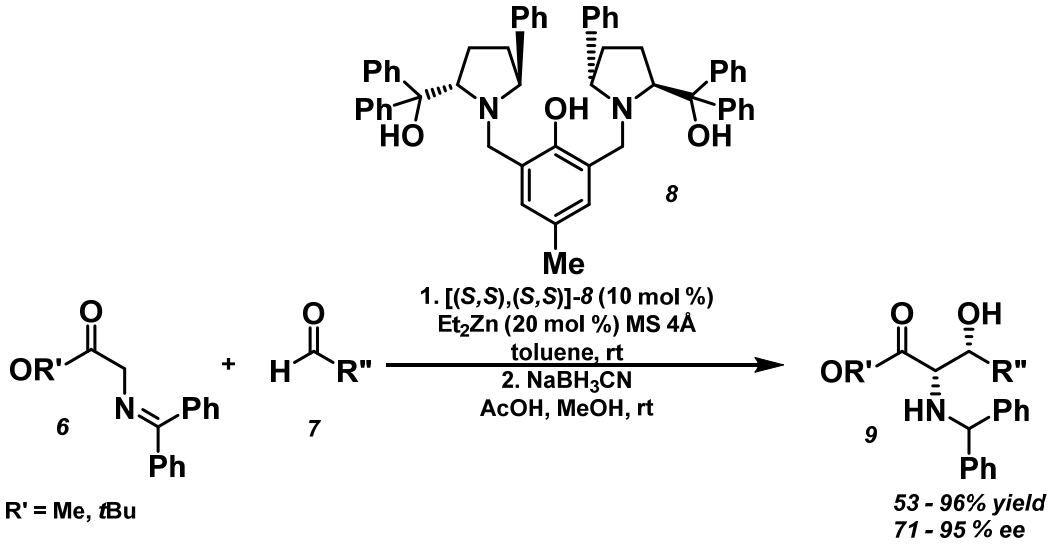


Figure 3. Synthesis of *Syn* β-Hydroxy α-Amino Esters

The final category of asymmetric syntheses is resolution. In a resolution, a racemic mixture is differentiated through chemical or physical means; the resulting product(s) can then be separated as enantiopure compounds. Resolutions fall into three classes; classical resolution, chiral chromatography, and kinetic resolution. Classical chiral resolution involves the use of a stoichiometric amount of a chiral resolving agent. In the Eli Lilly synthesis of duloxetine[5] (figure **4**), the starting material, (±)-**12**, is first resolved using (*S*)-mandelic acid.

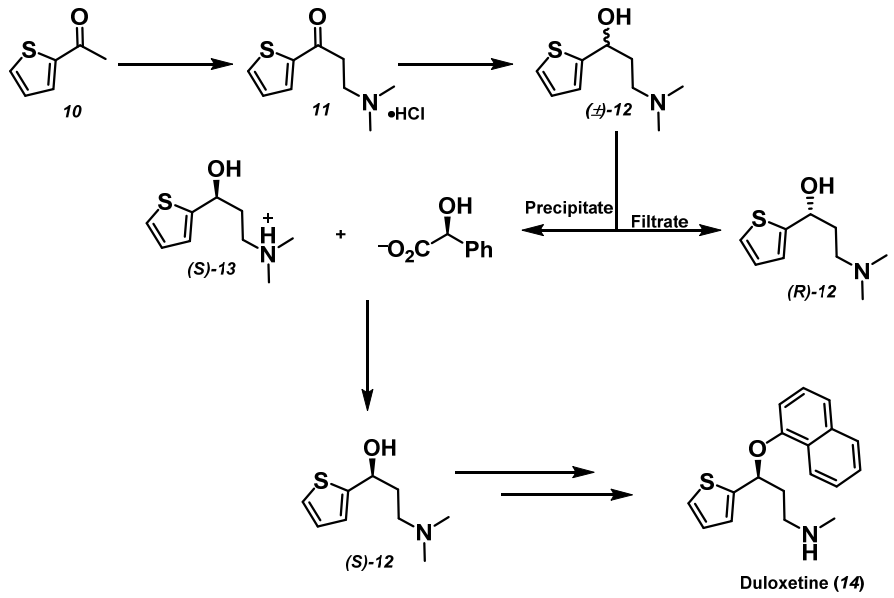


Figure 4. Eli Lilly's Synthesis of Duloxetine

(*S*)-Mandelic acid is reacted with compound **12** to yield salt **13** and enantioenriched (*R*)-**12**. Compound **13** is then reacted with base to yield the other enantiomer, (*S*)-**12**, which can then be used to synthesize duloxetine (**14**). This approach is most useful for amines and carboxylic acids as salt formation is straightforward.

Chiral chromatography relies on the use of a chiral stationary phase to resolve enantiomers in a mobile phase. While chiral chromatography is frequently used for analysis, chiral chromatography as part of a synthesis is not ideal. This is due to the large solvent volumes, long separation times, and high costs of the chiral stationary phases.

The final class of resolution we will examine is kinetic resolution. Kinetic resolutions distinguish the enantiomers of a racemic mixture with the use of a

chiral catalyst or reagent. The chiral catalyst or reagent promotes selective reaction of one enantiomer over the other yielding enantioenriched product as well as enantioenriched, unreacted starting material.

A kinetic resolution (figure **5**) takes advantage of the different rates of reaction of two enantiomers in a racemic mixture with a chiral reagent or catalyst.

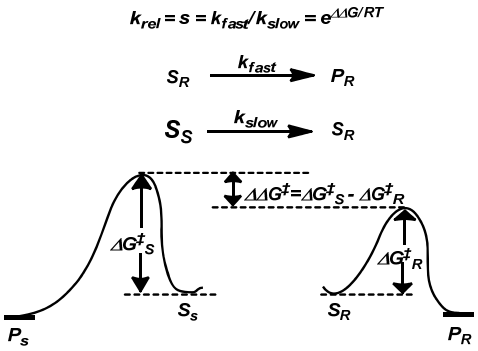


Figure 5. Relative Rates of Reaction

As seen in figure 5, the relative rates of reaction for the substrate enantiomers, S_R *and* S_S, is dictated by the difference in the activation energies of each enantiomer of the rate limiting step ($\Delta\Delta G^{\ddagger}$). Due to the difference of rates, up to a 50% yield of either the new product or the recovered starting material can be obtained with up to 100% enantiomeric excess (ee). The ee of the substrate or product changes as a function of conversion; as seen in figure 6, the substrate's ee will increase as conversion increases.

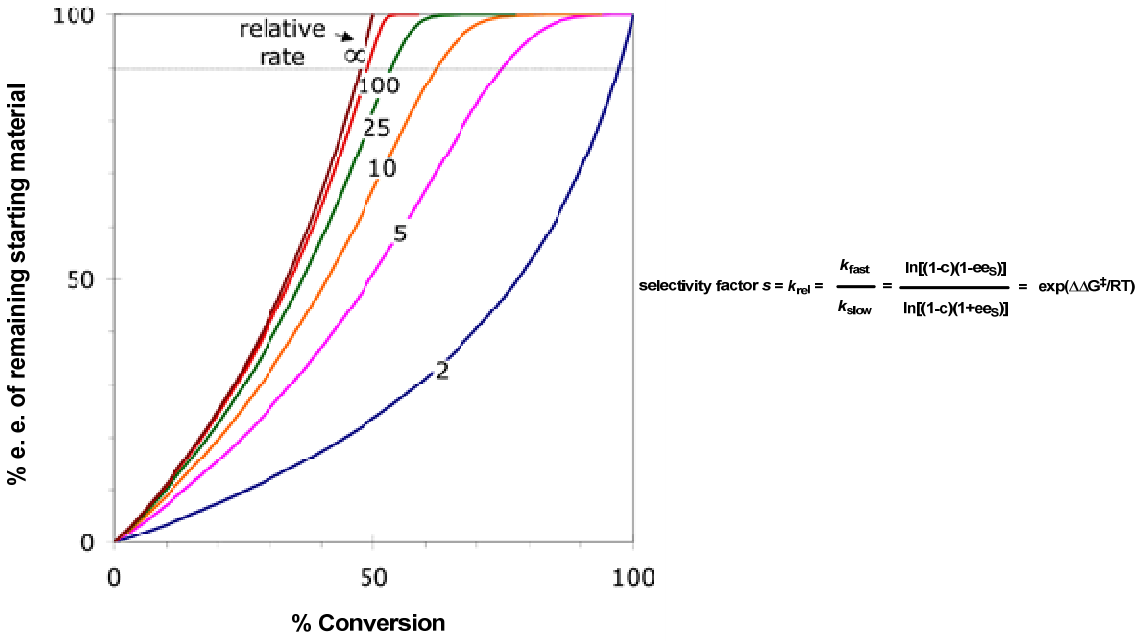


Figure 6. Conversion vs %ee

Another facet of kinetic resolution is the selectivity factor *s*. As seen in table 1, a set of representative values[6] of k_{rel} and $\Delta\Delta G^{\ddagger}$ show the extent of conversion needed to achieve 90, 98, and 99% ee of recovered unreacted starting material. The k_{rel} or *s* (equation in figure **6**) can help determine how selective a kinetic resolution may be and whether it is a valuable reaction. Due to the changes in enantiomeric excess as conversion increases, *s* factors can provide more consistent information.

Table 1. Representative k_{rel} with % Conversion Required for High Enantiomeric Excess

		Conversion (%) required to achieve:		
k_{rel}	$\Delta\Delta G^{\ddagger}$ (kcal/mol)	***90% ee***	***95% ee***	***99% ee***
1.5	0.24	99.9	99.99	>99.999
2	0.41	97.2	99.5	>99.7
5	0.95	74.8	84.0	>86.6
10	1.35	62.1	69.7	>72.1
50	2.31	50.4	54.0	>54.9
100	2.72	48.9	51.8	>52.4
500	3.66	47.7	50.0	>50.3

Kinetic resolutions have been used in multiple experimental situations including but not limited to: acylative/deacylative resolutions, oxidative kinetic resolutions, reductive kinetic resolutions, organometallic kinetic resolutions, and kinetic resolution of epoxides via nucleophilic ring opening. The first kinetic resolution was done by Marckwald and McKenzie (figure **7**)[7] when they observed enantioselective esterification by heating racemic mandelic acid (**15**) with (–)-menthol (**16**).

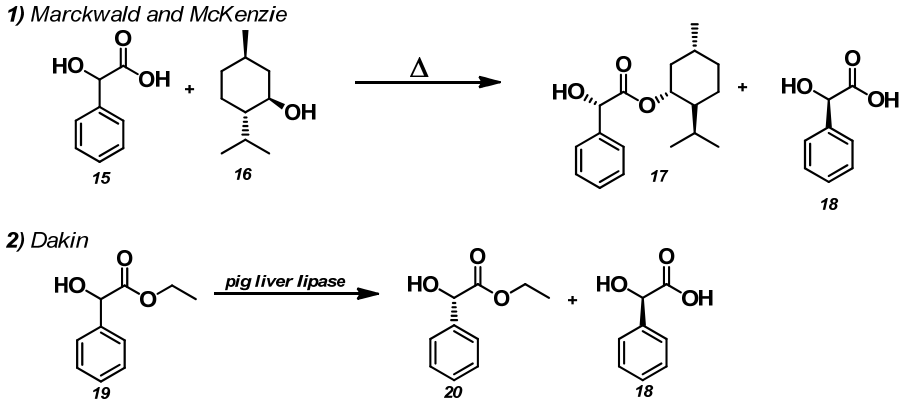


Figure 7. The First Kinetic Resolutions

They were able to recover a small amount of L-mandelic acid (**18**) after recrystallization. The first published kinetic resolution was done by Dakin (figure **7**)[8] in 1904 using crude pig liver lipase to resolve racemic ethyl mandelate (**19**) through hydrolysis.

1.2 Brønsted Acid Catalysts

Carbonyl activation plays an important role in organic synthesis. Chiral acids have, in recent years[9], become a focus of asymmetric syntheses and Brønsted acid catalysts (figure **8**) have been used in achiral synthesis as carbonyl activators.

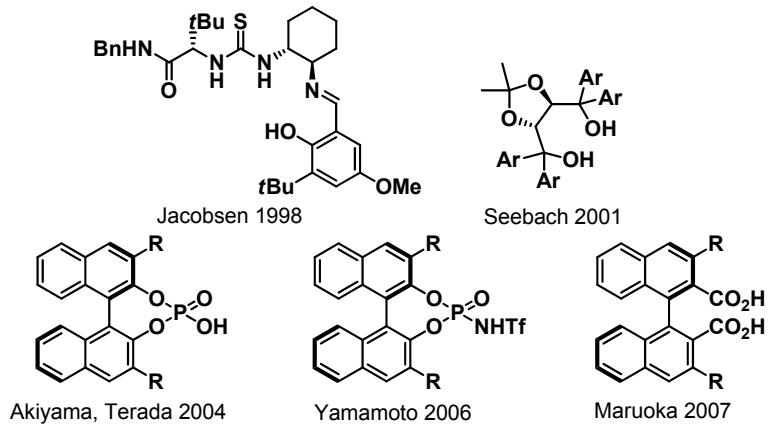


Figure 8. Chiral Brønsted Acids

New chiral diols and hydrogen bond donors were developed that displayed the ability to induce high diastereo- and enantioselectivity. The catalysts developed were originally used in Diels-Alder and Mukaiyama aldol reactions (figure **9**). Under these conditions, the activated carbonyl reacted with very strong nucleophiles and only required slightly acidic catalysts.

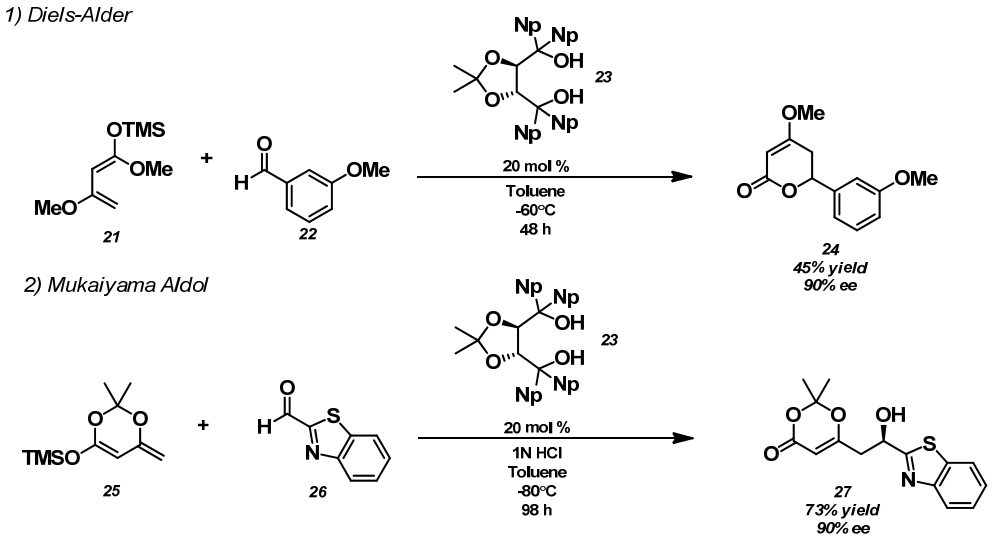
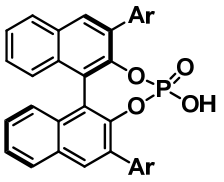
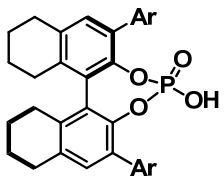


Figure 9. Chiral Diols Used in Synthesis

In 2004, axially chiral 1,1'-bi-2-naphthol (BINOL) phosphoric acid derived catalysts where developed by the Akiyama and Terada groups[10]. These catalysts (figure **10**) were primarily used in reactions in which the catalyst activated reactive electrophiles such as aldimines, ketimines, and aziridines.



28a Ar = 4-(*t*Bu)-C_6H_4
28b Ar = 9-phenanthryl
28c Ar = 2,4,6-(*i*Pr)$_3$-C_6H_2
28d Ar = 2,6-(*i*Pr)$_{2\text{-}4}$-(9-anthryl)-C_6H_2
28e Ar = Ph
28f Ar = 1-naphthyl
28g Ar = 2,6-(*i*Pr)$_{2\text{-}4}$-(*t*Bu)-C_6H_2
28h Ar = 9-anthryl
28i Ar = $SiPh_3$
28j Ar = 2,4-$(CF_3)_2$-C_6H_3



29a Ar = 2,4-$(CF_3)_2$-C_6H_3
29b Ar = $SiPh_3$
29c Ar = 3,5-$(CF_3)_2$-c_6H_3
29d Ar = 1-naphthyl
29e Ar = 4-Cl-C_6H_4
29f Ar = 1-pyrenyl
29g Ar = 2,4,6-Me_3-C_6H_2

Figure 10. Chiral BINOL Phosphoric Acid Catalysts

A few years later it was found that substrates with less basic functionalities were able to be activated by these BINOL derived phosphoric acid catalysts. Yamamoto and group[11] uncovered more acidic chiral Brønsted acids based on the BINOL phosphoric acid catalyst. These catalysts (figure **11**) have replaced the hydroxyl group with a triflylamide moiety. The strong electron withdrawing character of the new substituent significantly increased the acidity of the catalyst.

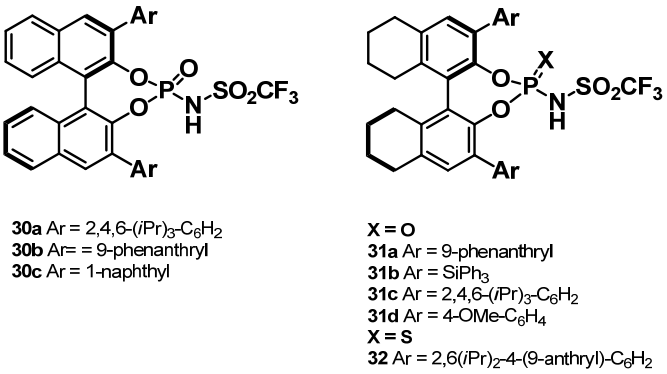


Figure 11. *N*-Triflylphosphoramides

The above catalysts have several features that are important to activation (figure **12**).

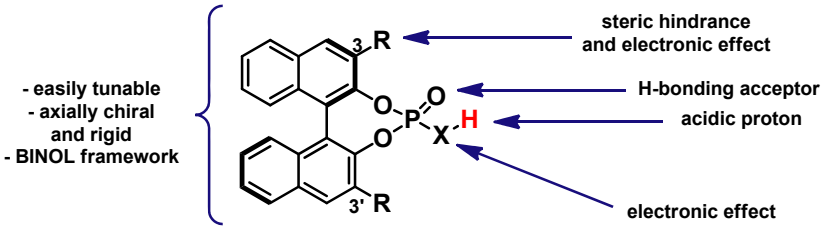


Figure 12. Features of Chiral BINOL Phosphoric Acid Catalysts

The BINOL backbone is the core structure of the catalyst. It is axially chiral and rigid. The core structure is modified by substituents placed at the 3 and 3' positions. These substituents add steric hindrance and electronic effects to the catalyst. The substituents shield the active site to allow for specificity. The catalyst also possesses an acidic proton and a phosphoryl oxygen that can act as a hydrogen bond acceptor. The catalysts activate the substrate by one of two modes (figure **12**).

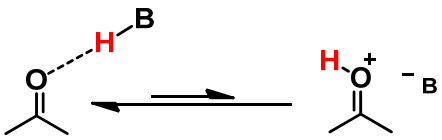


Figure 13. Carbonyl Activation

The first is through a direct hydrogen bonding event between the substrate carbonyl oxygen and the acidic proton of the catalyst. The second mode is through a contact ion pair where the carbonyl oxygen of the substrate takes the acidic proton from the catalyst. The second mode is less likely and it has been predicted that activation is most likely a combination of the two modes. The pK_a difference between the catalyst and the substrate determines which activation mode is the most populated in equilibrium.

1.3 Small Molecule Synthesis

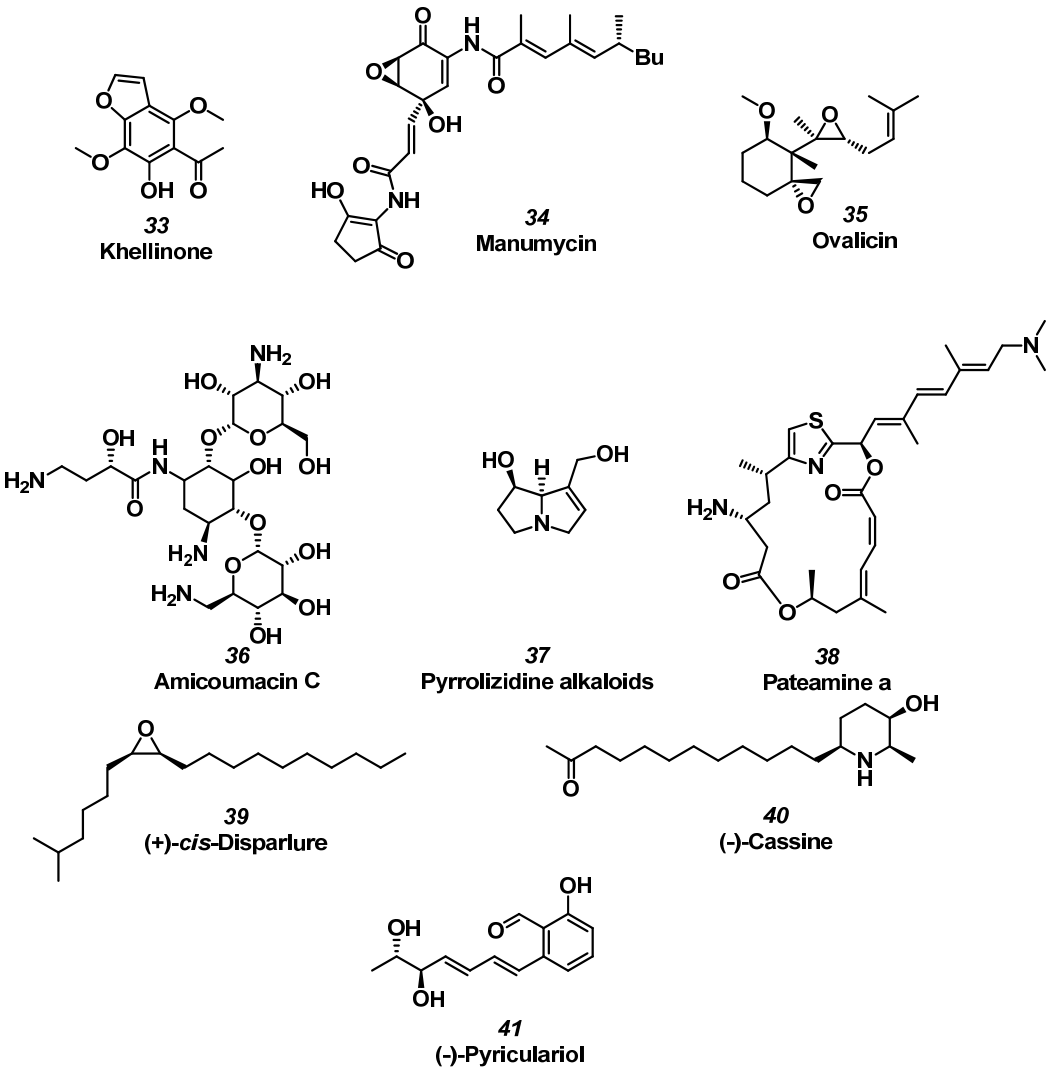


Figure 14. Natural Products Synthesized via Small Molecules

An important facet of organic synthesis is the development of pathways to small molecules. These small molecules, especially those that are stereochemically enriched, can be used in the production of larger, more complex, chiral molecules. Many reviews have been written on the use of small

molecules in enantioselective syntheses. In 2004, a review was written by Tom Pettus[12] detailing the use of four cyclohexadienone ketals and quinols (figure **14**) in enantioselective syntheses of natural products.

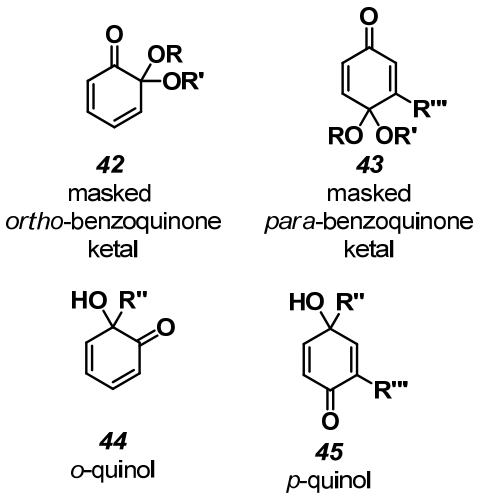


Figure 15. Cyclohexadienone Building Blocks

Compounds similar to **42** have been used in the synthesis of khellinone[13] (**33**, figure **14**), CP-263,411[14], calicheamicinone[15], ryanodol[16], a derivative of forsythide[17], and colchicines[18]. The ketal **43** has been used in the synthesis of five natural product families: manumycins (**34**, figure **14**), huperizes, torreyanoids, diepoxins, and illudines[19]. Compound **44**-like substrates have been used in the synthesis of calicheamicinone[20], ovalicin[21] (**35**, figure **14**), aerothionin and homoaerothionin[22], trichodimerol[23], and tricycloillicinone[24]. *P*-quinol derivatives (**45**) have been used in the synthesis of griseofulvinoids, futoquinoids, sorbicillinoids, and ananorosinoids[25].

A review of β-lactams as small molecule building blocks was published in 2007[26]. Since the discovery of penicillin, antibiotics with the β-lactam skeletal structure have been the subject of discussion and interest. β-Lactams can be used in the synthesis of mono-, bi-, and polycyclic 3 to 6 membered heterocycles as well as macrocyclic heterocycles[27] (figure **15**).

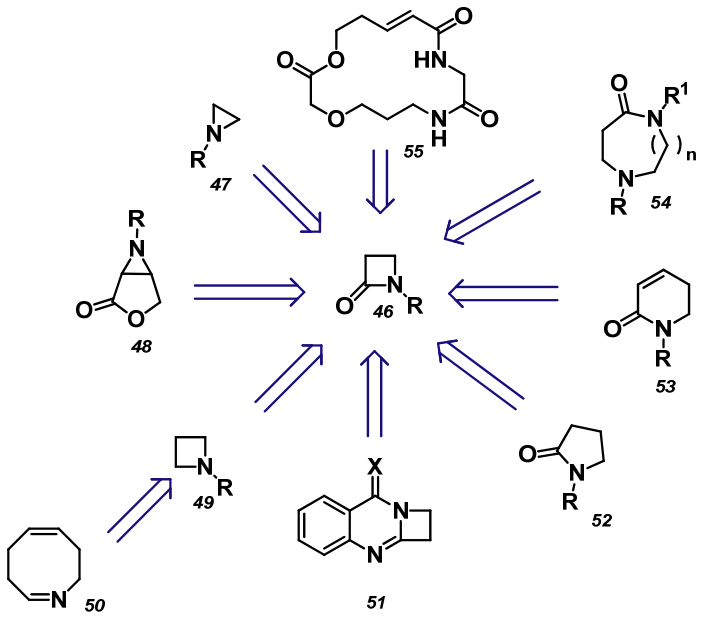


Figure 16. β-Lactam Building Block

2-Azetidinone (**46**) is the core of the β-lactam structure. It has four easy-to-break bonds resulting from bond and angle strain. The strained bonds and unique bond angles have allowed this structure to become a synthetically useful building block.

A more recent review[28] compiled by Reddy and coworkers identifies the recent boost in the use of δ-hydroxy α,β-unsaturated aldehydes. The many

functionalities and ability to selectively manipulate each position have led this compound to be highly studied. δ-Hydroxy α,β-unsaturated aldehydes, further known as Perlin aldehydes, are compounds derived from glycal, a term for cyclic enol ethers that contain a double bond between carbons 1 and 2. Perlin aldehydes have been used in stereoselective synthesis of various cyclic and acyclic building blocks as well as naturally occurring compounds such as sex pheromones, cofactors, sphingosine derivatives, metabolites, (-)-cassine (**40**, figure **14**), piperidine alkaloids, phytotoxins, and nucleosides.

1.4 Conclusion

Natural products are continuously tested for biological activity. Compounds that show activity are of interest to scientists; however, due to the often small amount produced by the natural source, synthetic chemists have a considerable need to develop new methodologies to prepare these compounds in sufficient quantities. One of the many ways to prepare natural products synthetically is through small molecules. Small molecules can be perfect precursors with set chirality as well as easily manipulated functionalities. First, however, the small molecules must be made. The next two chapters will discuss how kinetic resolution and Brønsted acid catalysts can be used to yield enantiopure small molecules that can be used in the synthesis of natural products.

1.5 References

1. a) Ariëns, E. J., Stereochemistry, a Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical Pharmacology. *Eur. J. Clin. Pharmacol.* **1984,** *26*, 663; b) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roxzkowski, A.; Tomolonis, A.; Fried, J. H., Nonsteroidal Antiinflammatory Agents. I. 6-Substituted 2-Naphthylacetic Acids. *J. Med. Chem.* **1970,** *13*, 203; c) Kean, W. F.; Lock, C. J. L.; Rischke, J.; Butt, R.; Buchanan, W. W.; Howard-Lock, H., Effect of *R* and *S* Enantiomers of Naproxen on Aggregation and Thromboxane Production in Human Platelets. *J. Pharm. Sci* **1989,** *78*, 324; d) Shen, T. Y., Perspectives in Nonsteroidal Anti-Inflammatory Agents. *Angew. Chem. Int. Ed.* **1972,** *11*, 460.

2. Keith, J. M.; Larrow, J. F.; Jacobsen, E. N., Practical Considerations in Kinetic Resolution Reactions. *Adv. Synth. Catal.* **2001,** *343*, 5.

3. Ananthan, B.; Chang, W. C.; Lin, J. S.; Li, P. H.; Yan, T. H., A C_2-Symmetric Chiral Pool-Based Flexible Strategy: Synthesis of (+)- and (—)-Shikimic Acids, (+)- and (—)-4-*epi*-Shikimic Acids, and (+)- and (—)-Pinitol. *J. Org. Chem.* **2014,** *79*, 2898.

4. Trost, B. M.; Miege, F., Development of ProPhenol Ligands for the Diastereo- and Enantioselective Synthesis of ß-Hydroxy-α-amino Esters. *J. Am. Chem. Soc.* **2014,** *136*, 3016.

5. Fujima, Y.; Ikunaka, M.; Inoue, T.; Matsumoto, J., Synthesis of (*S*)-3-(*N*-Methylamino)-1-(2-thienyl)propan-1-ol: Revisiting Eli Lilly's Resolution-Racemization-Recycle Synthesis of Duloxetine for Its Robust Processes. *Org. Process Res. Dev.* **2006,** *10,* 905.

6. Vedejs, E.; Jure, M., Efficiency in Nonenzymatic Kinetic Resolutions. *Angew. Chem. Int. Ed.* **2005,** *44,* 3974.

7. Marckwald, W.; McKenzie, A., Ueber eine principiell neue Methode zur Spaltung racemischer Verbindungen in die activen Bestandtheile. *Ber. Dtsch. Chem. Ges.* **1899,** *32,* 2130.

8. Dakin, H. D., The hydrolysis of optically inactive esters by means of enzymes: Part I. The action of lipase upon esters of mandelic acid. The resolution of inactive mandelic acid. *J. Physiol.* **1904,** *30,* 253.

9. a) Rueping, M.; Kuenkel, A.; Atodiresei, I., Chrial Brønsted acids in enantioselective carbonyl activations — activation modes and applications. *Chem. Soc. Rev.* **2011,** *40,* 4539; b) Kampen, D.; Reisinger, C. M.; List, B., Chiral Brønsted Acids for Asymmetric Organocatalysis. *Top. Curr. Chem.* **2010,** *291,* 395.

10. a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K., Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem. Int. Ed.* **2004,** *43,* 1566; b) Uraguchi, D.; Terada, M., Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004,** *126,* 5356.

11. a) Nakasima, D.; Yamamoto, H., Design of Chiral *N*-Triflyl Phosphoramide as a Strong Chiral Brønsted Acid and Its Applications to Asymmetric Diels—Alder Reaction. *J. Am. Chem. Soc.* **2006,** *128,* 9626; b) Cheon, C. H.; Yamamoto, H., Super Brønsted acid catalysis. *Chem. Commun.* **2011,** *47,* 3043.

12. Magdziak, D.; Meek, S. J.; Pettus, T. R. R., Cyclohexadienone Ketals and Quinols: Four Building Blocks Potentially Useful for Enantioselective Synthesis. *Chem. Rev.* **2004,** *104,* 1383.

13. Gammill, R. B., Total synthesis of khellinone and khellin the pyrogallol route regiospecific methoxylation of a benzofuran. *Tetrahedron Lett.* **1985,** *26,* 1385.

14. Njardarson, J. T.; McDonald, I. M.; Spiegel, D. A.; Inoue, M.; Wood, J. L., An Expeditious Approach toward the Total Synthesis of CP-263,114. *Org. Lett.* **2001,** *3,* 2435.

15. Churcher, I.; Hallett, D.; Magnus, P., Synthesis of the Enediyne Aglycon (±)-Calicheamicinone. *J. Am. Chem. Soc.* **1998,** *120,* 3518.

16. a) Deslongchamps, P. B., A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; MacLachlan, F.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P., The total synthesis of (+)-ryanodol. Part I. General strategy and search for a convenient diene for the construction of a key tricyclic intermediate. *Can. J. Chem.* **1990,** *68,* 115; b) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.;

Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; MacLachlan, F.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P., The total synthesis of (+)-ryanodol. Part II. Model studies for rings B and C of (+)-anhydroryanodol. Preparation of a key pentacyclic intermediate. *Can. J. Chem.* **1990,** *68,* 127.

17. Liao, C. C.; Wei, C. P., Synthetic applications of masked o-benzoquinones. A novel total synthesis of (±)forsythide aglucone dimethyl ester. *Tetrahedron Lett.* **1989,** *30,* 2255.

18. Banwell, M. G.; Lambert, J. N.; Mackay, M. F.; Greenwood, R. J., A biomimetic and fully regiocontrolled total synthesis of (±)-colchicine. *J. Chem. Soc., Chem. Commun.* **1992,** 974.

19. a) Wipf, P.; Coish, P. D. G., Total Synthesis of (±)-Nisamycin. *J. Org. Chem.* **1999,** *64*, 5053; b) Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K., Manumycin A: Synthesis of the (+)-Enantiomer and Revision of Stereochemical Assignment. *J. Org. Chem.* **1998,** *63*, 3526; c) Kapfer, I.; Lewis, N. J.; Macdonald, G.; Taylor, R. J. K., The synthesis of novel analogues of the manumycin family of antibiotics and the antitumour antibiotic LL-C10037α. *Tetrahedron Lett.* **1996,** *37*, 2101; d) Högenauer, K.; Baumann, K.; Mulzer, J., Synthesis of (±)-desamino huperzine A. *Tetrahedron Lett.* **2000,** *41*, 9229; e) Li, C.; Lobkovsky, E.; Porco, J. A., Total Synthesis of (±)-Torreyanic Acid. *J. Am. Chem. Soc.* **2000,** *122*, 10484; f) Franck-Neumann, M.; Miesch, M.; Barth, F.,

Synthese cyclopropenique de derives de l'illudine M. *Tetrahedron Lett.* **1989,** *30*, 3537; g) Wipf, P.; Jung, J. K.; Rodríguez, S.; Lazo, J. S., Synthesis and biological evaluation of deoxypreussomerin A and palmarumycin CP_1 and related naphthoquinone spiroketals. *Tetrahedron* **2001,** *57*, 283.

20. Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J., Total synthesis of calicheamicinone: a solution to the problem of the elusive urethane. *J. Am. Chem. Soc.* **1990,** *112*, 3253.

21. Corey, E. J.; Dittami, J. P., Total synthesis of (±)-ovalicin. *J. Am. Chem. Soc.* **1985,** *107*, 256.

22. a) Boehlow, T. R.; Harburn, J. J.; Spilling, C. D., Approaches to the Synthesis of Some Tyrosine-Derived Marine Sponge Metabolites: Synthesis of Verrongamine and Purealidin N. *J. Org. Chem.* **2001,** *66*, 3111; b) Nishiyama, S.; Yamamura, S., Total Synthesisi of (±)-Aerothionin, (±)-Homoaerothionin, and (±)-Aerophobin-1. *Bull. Chem. Soc. Jpn.* **1985,** *58*, 3453.

23. a) Abe, N.; Sugimoto, O.; Arakawa, T.; Tanji, K. I.; Hirota, A., Sorbicillinol, a Key Intermediate of Bisorbicillinoid Biosynthesis in trichoderma sp. USF-2690. *Biosci. Biotechnol. Biochem.* **2001,** *65*, 2271; b) Barnes-Seeman, D.; Corey, E. J., A Two-Step Total Synthesis of the Natural Pentacycle Trichodimerol, a Novel Inhibitor of TNF-α Production. *Org. Lett.* **1999,** *1*, 1503; c) Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A., Biomimetic Explorations Towards the Bisobicillinoids:

Total Synthesis of Bisorbicillinol, Bisorbibutenolide, and Trichodimerol. *Angew. Chem. Int. Ed.* **1999,** *38*, 3555.

24. Pettus, T. R. R.; Chen, X. T.; Danishefsky, S. J., A Fully Synthetic Route to the Neurotrophic Illicinones by Sequential Aromatic Claisen Rearrangements. *J. Am. Chem. Soc.* **1998,** *120*, 12684.

25. a) MacMillan, J., Griseofulvin. Part XIV. Some alcoholytic reactions and the absolute configuration of griseofulvin. *J. Chem. Soc.* **1959**, 1823; b) Katoh, T.; Ohmori, O., Studies toward the total synthesis of Sch 202596, an antagonist of the galanin receptor subtype GaIR1: synthesis of geodin, the spirocoumaranone subunit of Sch 202596. *Tetrahedron Lett.* **2000,** *41*, 465; c) Feringa, B.; Wynberg, H., Oxidative phenol coupling with cupric-amine complexes. *Tetrahedron Lett.* **1979,** *18*, 4447; d) Shizuri, Y.; Nakamura, K.; Yamamura, S.; Ohba, S.; Yamashita, H.; Saito, Y., Total syntheses of isodihydrofutoquinol a, futoquinol, and isofutoquinol A and B. *Tetrahedron Lett.* **1986,** *27*, 727; e) McKillop, A.; McLaren, L.; Watson, R. J.; Taylor, R. J. K.; Lewis, N., A concise synthesis of the novel antibiotic aranorosin. *Tetrahedron Lett.* **1993,** *34*, 5519; f) Hara, H.; Inoue, T.; Nakamura, H.; Endoh, M.; Hoshino, O., A novel feautre in phenyliodine diacetate oxidation. *Tetrahedron Lett.* **1992,** *33*, 6491; g) Taub, D.; Kuo, C. H.; Slates, H. L.; Wendler, N. L., A total synthesisi of griseofulvin and its optical antipode. *Tetrahedron* **1963,** *19*, 1; h) Danishefsky, S.; Walker, F. J., A stereospecific synthesis of griseofulvin. *J. Am. Chem. Soc.* **1979,** *101*, 7018; i) Wipf, P.; Kim, Y.; Fritch, P. C., Total synthesis and structure

assignment of the antitumor antibiotic aranorosin. *J. Org. Chem.* **1993,** *58*, 7195; j) Pettus, L. H.; Van De Water, R. W.; Pettus, T. R. R., Synthesis of (±)-Epoxysorbicillinol Using a Novel Cyclohexa-2,5-dienone with Synthetic Applications to Other Sorbicillin Derivatives. *Org. Lett.* **2001,** *3*, 905.

26. Alcaide, B.; Almendros, P.; Aragoncillo, C., ß-Lactams: Versatile Building Blocks for the Stereoselective Synthesis of Non-ß-Lactam Products. *Chem. Rev.* **2007,** *107*, 4437.

27. a) Van Brabandt, W.; Dejaegher, Y.; Van Landeghem, R.; De Kimpe, N., Reduction of 4-(Haloalkyl)azetidin-2-ones with $LiAlH_4$ as a Powerful Method for the Synthesis of Stereodefined Aziridines and Azetidines. *Org. Lett.* **2006,** *8* 1101; b) Sammes, P. G.; Smith, S., Preparation of azetidines from 1,3 aminopropanols. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2415; c) Alajarín, M.; Molina, P.; Vidal, Á.; Tovar, F., The First Aza-Wittig Reaction of the ß-Lactam Carbonyl Group. *Synlett* **1998**, 1288; d) Moloney, M. G., Excitatory amino acids. *Nat. Prod. Rep.* **1999,** *16*, 485; Alcaide, B.; Martin-Cantalejo, Y.; Perez-Castells, J.; Rodriguez-Lopez, J.; Sierra, M. A.; Monge, A.; Perez-Garcia, V., Stereoselective preparation of mono- and bis-ß-lactams by the 1,4-diaza-1,3-diene - acid chloride condensation: scope and synthetic applications. *J. Org. Lett.* **1992,** *57*, 5921; e) Gardner, B.; Nakanishi, H.; Kahn, M., Conformationally constrained nonpeptide ß-turn mimetics of enkephalin. *Tetrahedron* **1993,** *49*, 3433; f) Crombie, L.; Jones, R. C. F.; Osborne, S.; Mat-Zin, A. R., Medium ring heterocycles: transamidation reactions of ß-lactams. *J. Chem. Soc., Chem.*

Commun. **1983**, 959; g) Vidya, R.; Eggen, M.; Nair, S. K.; Georg, G. I.; Himes, R. H., Synthesis of Cryptophycins via an *N*-Acyl-ß-lactam Macrolactonization. *J. Org. Chem.* **2003,** *68*, 9687.

28. Reddy, V. R.; Kumar, V.; Sagar, R.; Shaw, A. K., Glycal-Derived δ-Hydroxy α,ß-Unsaturated Aldehydes (Perlin Aldehydes): Versatile Building Blocks in Organic Synthesis. *Chem. Rev.* **2013,** *113*, 3605.

CHAPTER II

FACILE SYNTHESIS OF ENANTIOENRICHED α-SUBSTITUTED γ-HYDROXY *TERT*-BUTYL ESTERS

2.1 Background

The lactone functional group is becoming of increasing importance to the medicinal field. It is a common motif in various biologically active compounds. Most lactone functional groups contain a chiral center whose configuration must be set properly for bioactivity. Current asymmetric synthetic strategies involve expensive chiral auxiliaries to install chiral centers[1], inclusion-type reactions that involve crystals and microbes[2], and installing stereocenters early in the synthesis[3]. The problem with installing stereocenters early on is that one has to take into consideration how certain reactions later in the synthesis will change the stereocenter. There is a need for asymmetric syntheses that do not involve too many expensive reagents, reagents that cannot be removed easily, or excessive steps.

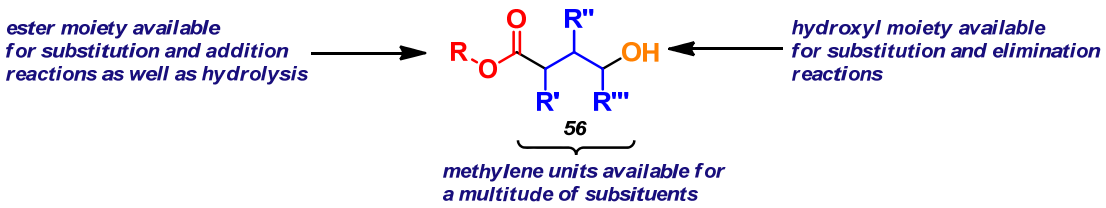


Figure 17. Skeletal Structure of the Hydroxy Ester Substrate

Enantioenriched hydroxy esters of the form **56** (figure **16**) contain two distinct functionalities that can be easily manipulated (shown in red and orange). This leads compounds such as **56** to be versatile building blocks. Previous syntheses of these molecules are virtually nonexistent. This is likely due to the tendency of non-bulky esters to lactonize or epimerize. Two examples are a hydroboration/oxidation (figure **18**) of an α-substituted allylic ester prepared by an asymmetric copper catalyzed S_N2'-addition[4] and an organocatalyzed Friedel-Crafts alkylation of an α,β-unsaturated ester/aldehyde (figure **19**) followed by reduction[5].

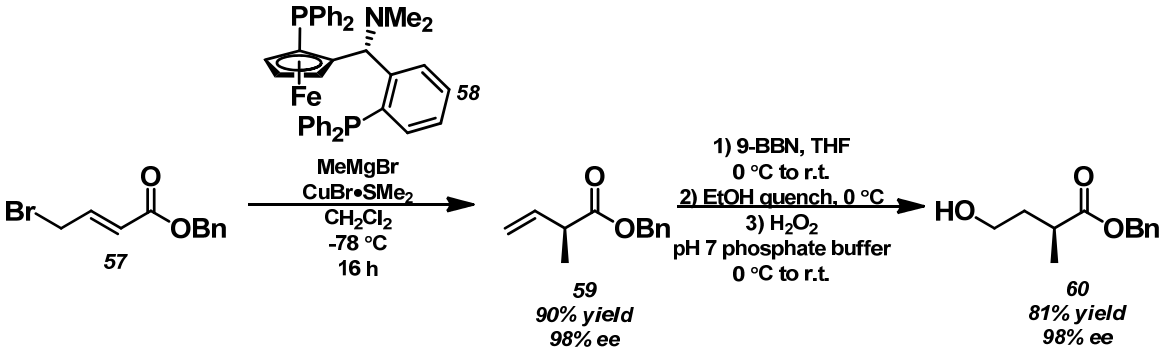


Figure 18. Copper-Catalyzed S_N2 Addition

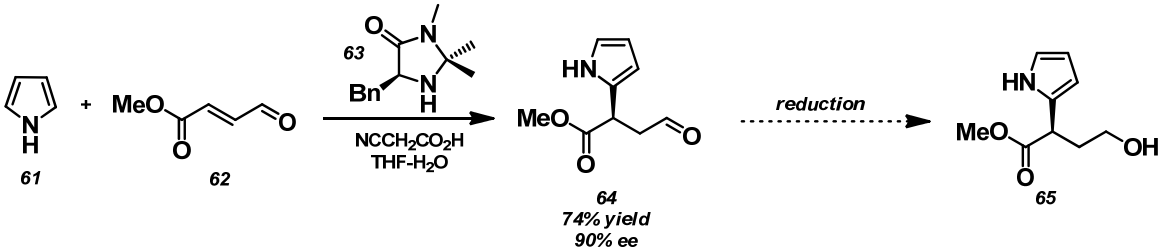


Figure 19. Friedal-Crafts Alkylation

Stabilization of these hydroxy esters through the use of a bulky ester and an enantioselective synthesis will allow the wide spread use of these building blocks in the construction of important biologically active molecules.

The strategy for the preparation of these versatile building blocks takes advantage of the different rates of reaction of both enantiomers in the presence of a chiral Brønsted acid catalyst (Figure **20**).

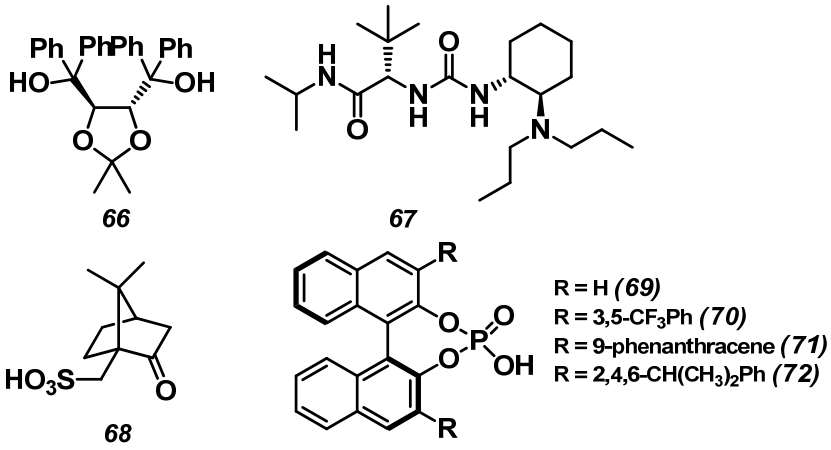


Figure 20. Chiral Brønsted Acid Catalysts

By using bulky esters, the instability of the substrates is reduced allowing for slower reaction times and decreased reactivity such that the reaction will only happen in the presence of a strongly activating acid catalyst (figure **21**). The two enantiomers can then be separated via the selective lactonization of one enantiomer over the other.

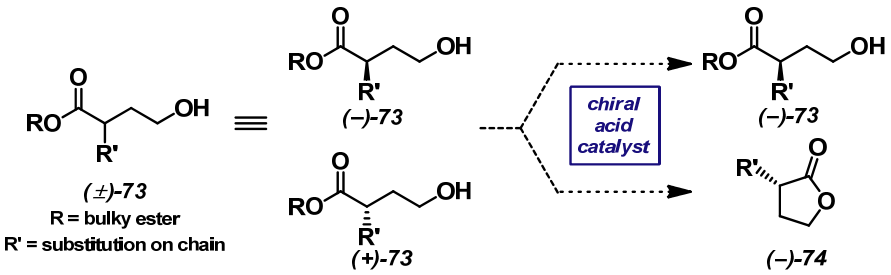
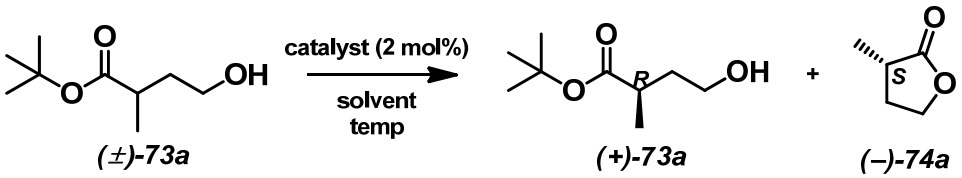


Figure 21. Kinetic Resolution of a Hydroxy Ester with a Chiral Catalyst

2.2 Results and Discussion

Initial optimization of the kinetic resolution was completed by Petersen group lab member, Ghassan Qabaja, using α-methyl hydroxy *tert*-butyl ester **73a** (Table **2**).

Table 2. Initial Optimization



entry	catalyst	solvent	temp (°C)	time (h)	% convn	% $ee_{SM\ (1a)}$	% $ee_{P\ (2a)}$	s	
1	66	CH_2Cl_2	5	6	3	0	0	n/a	
2	67	CH_2Cl_2	5	6	18	0	0	n/a	
3	68	CH_2Cl_2	5	12	1	0	n/a	n/a	
4	69	CH_2Cl_2	5	19	75	0	0	n/a	*catalyst screen*
5	70	CH_2Cl_2	5	24	71	17	32	1	
6	71	CH_2Cl_2	5	24	23	8	29	4	
7	72	CH_2Cl_2	5	24	40	58	31	25	
8	72	toluene	5	24	41	64	41	19	
9	72	THF	5	48	2	0	n/a	n/a	*solvent screen*
10	72	Et_2O	5	48	2	0	10	n/a	
11	72	toluene	–5	48	67	>98	32	15	*temperature screen*
12	72	toluene	–20	720	47	71	49	19	

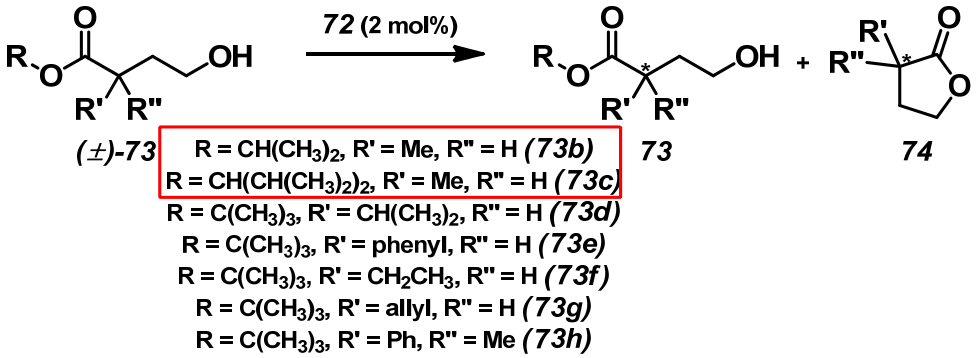
The hydroxy ester was cooled to 5 ˚C in dichloromethane and treated with a variety of chiral Brønsted acid catalysts. TADDOL and thiourea catalysts (table **2**, entries **1** and **2**) were unable to drive the reaction towards product. Camphor sulfonic acid (table **2**, entry **3**) and unsubstituted BINOL phosphoric acid (table **2**, entry **4**) were able to induce lactonization; however, no enantiomeric excess (ee) of either recovered starting material or lactone product was achieved. When 3,3'-substituted BINOL phosphoric acid catalysts (table **2**, entries **5**-**7**) were used, enantioenrichment of both the starting material and product was seen; with the triisopropyl phenyl catalyst showing the most selectivity. Catalyst **72** pushed the conversion to 40% yielding lactone **74a** with a 68% ee and recovered hydroxy ester **73a** with 57% ee giving a selectivity factor of 25.

A limited solvent screen (table **2**, entries **8**-**10**) was performed using both protic and aprotic solvents. Polar solvents such as tetrahydrofuran (THF) and diethyl ether (Et_2O) were ineffective in the lactonization. This is likely due to the interruption of hydrogen bonding between the catalyst and the substrate. Non-polar solvents dichloromethane, toluene, and hexanes allowed for conversion to product. A small temperature screen was carried out using toluene as the solvent. It was seen that temperature only affects the reaction time where low temperatures significantly increase reaction time. These optimized conditions allowed for consistent selectivity factors of ~20 with the test substrate **73a**.

With optimized conditions in hand, a substrate scope was developed and completed (Table **3**). The first substrates tested were those with different ester

functionalities. The smaller isopropyl ester **73b** (table **3**, entry **1**) showed severely reduced selectivity and reaction time. The bulkier 2,4-dimethyl-3-pentyl ester **73c** (table **3**, entry **2**) was exorbitantly slow and required heat to push conversion while showing low selectivity. This research revealed that the *tert*-butyl ester was the "Goldilocks" of the esters tested.

Table 3. Substrate Scope



	entry	substrate	solvent	temp (°C)	time (h)	% convn	% $ee_{SM\ (1)}$	% $ee_{P\ (2)}$	s
work of this thesis	1	73b	CH_2Cl_2	5	8	68	21	24	1.4
	2	73c	CH_2Cl_2	35	144	50	14	27	1.5
	3	73d	hexanes	5	72	56	52	37	3.9
	4	73e	toluene	5	40	71	50	26[a]	2.3
	5	73f	CH_2Cl_2	5→rt	336	62	85	n/a	8.1
	6	73g	CH_2Cl_2	5	72	63	86	50	7.9
	7	73h	CH_2Cl_2	5→rt	232	53	83	66	16.7

Conversion and % ee's determined by chiral GC analysis unless indicated otherwise.
[a]% ee's determined by HPLC.

To form the ester substrates, commercially available α-methyl-γ-butyrolactone (**75**) was opened with benzyl bromide (BnBr) and potassium hydroxide (KOH) in toluene at reflux. The intermediate was then saponified with

KOH in methanol:water (MeOH:H_2O, 1:0.5) at reflux to form carboxylic acid **76** (figure **22**).

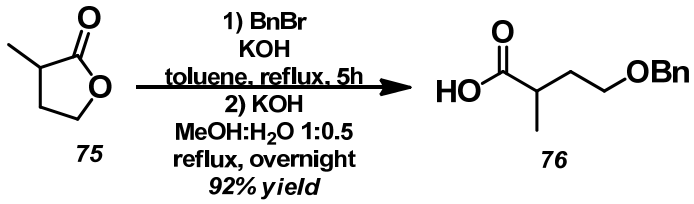


Figure 22. Opening of α-Methyl-γ-Butyrolactone

Acid/ether **76** was then esterified with a variety of alcohols. Thionyl chloride and isopropyl alcohol were reacted with **76** to form ester/ether **77**. Thionyl chloride is used to make the hydroxyl group a better leaving group allowing for esterification by isopropyl alcohol (figure **23**). Hydrogenolysis was then implemented with palladium hydroxide on carbon and gaseous hydrogen on the intermediate **77** to form ester **73b**; no yield was obtained on this reaction.

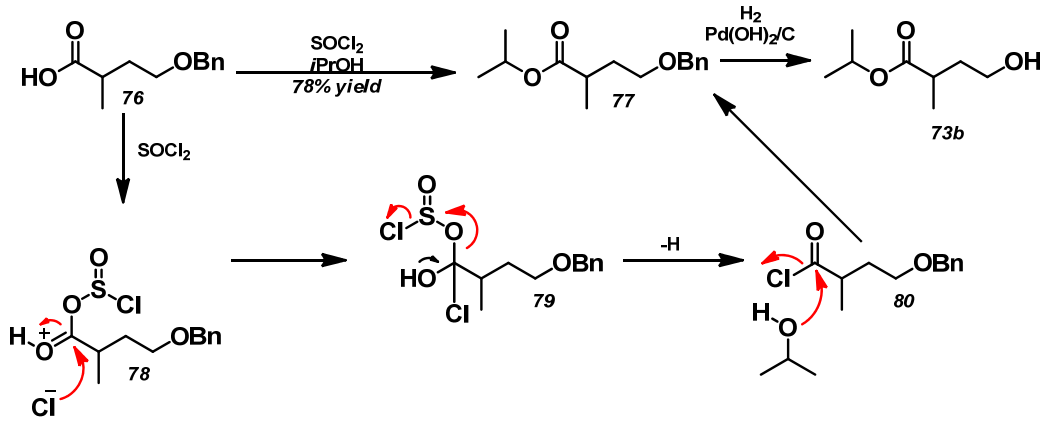


Figure 23. Formation of Intermediate 77

This ester performed poorly during lactonization with the chiral catalyst likely due to the ease with which the ester lactonizes in the absence of a catalyst. The next ester tested was a bulky ester. The first method for preparation attempted was a Steglich esterification[6] of diphenylcarbinol and **76** using *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane (figure **24**) to form the ester/ether **84**. Not surprisingly, upon hydrogenolysis, it was noticed that the diphenylcarbinol functionality was labile and would reduce to the carboxylic acid rather than the reduction to the hydroxy ester with removal of the benzyl group.

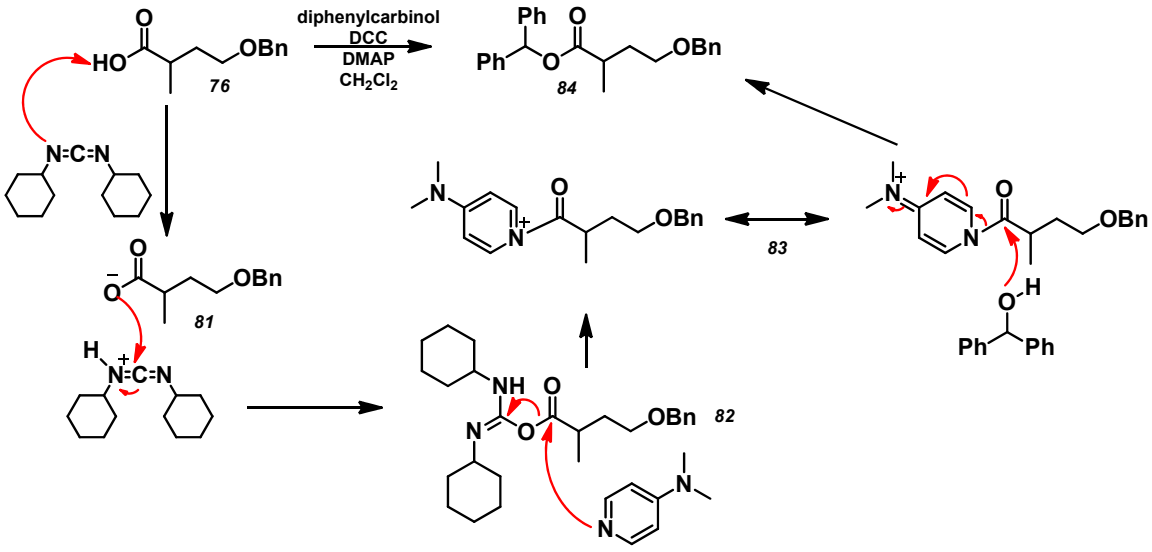


Figure 24. Formation of Intermediate 84

Another bulky alcohol was chosen for the esterification of **76** that would be orthogonal to the benzyl ether protecting group. Thus, diisopropylcarbinol was chosen and used in a Steglich esterification (figure **25**). The benzyl group of

ester/ether **85** was removed via hydrogenolysis with palladium hydroxide on carbon and gaseous hydrogen to afford hydroxy ester **73c** in a quantitative yield.

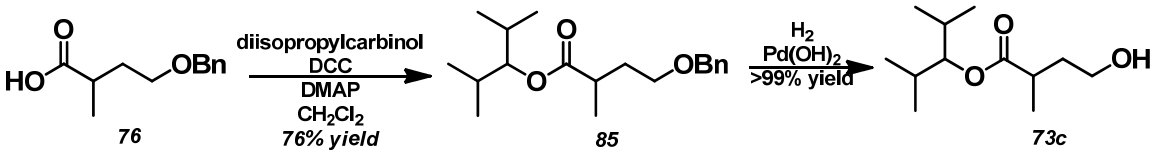


Figure 25. Formation of Intermediate 85

Petersen group lab members found that hydroxy esters with bulky α-substituents (table **3,** entries **3** and **4**, isopropyl **73d** and phenyl **73e**) were poor substrates in the resolution. Hydroxy esters with small to moderately-sized substituents (table **3**, entries **5** and **6**, ethyl **73f** and allyl **73g**) proceeded through the resolution with adequate to good selectivities. The α-allyl substrate yielded recovered starting material with good selectivity. The α,α-disubstituted hydroxy ester yielded good selectivity producing a challenging all-carbon quaternary center (table **3**, entry **7**, **73h**).

Another facet of this research is the desymmetrization of prochiral substrates (figure **26**) developed by Jennifer Wilent, a graduate student in the Petersen lab. In this set of experiments, a prochiral diester is reacted with a chiral catalyst to yield enantiopure lactone.

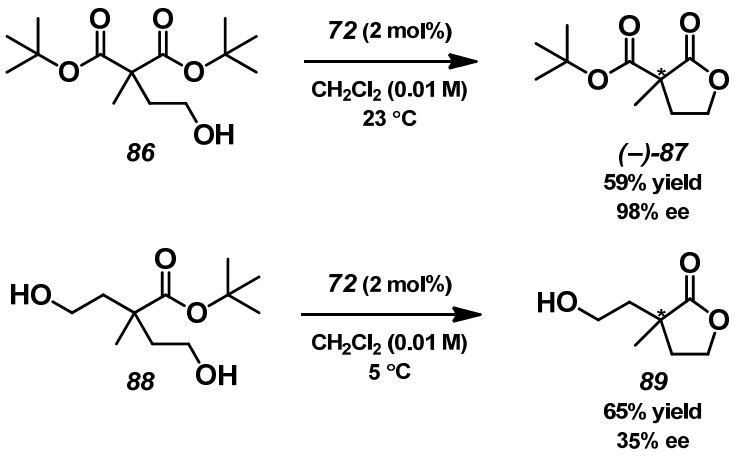


Figure 26. Desymmetrization of Prochiral Compounds

This variant of kinetic resolution is not limited by the same yield restraints. The symmetric substrates were able to be reacted under the optimized kinetic resolution conditions previously found. Prochiral diester **86** was converted to enantioenriched lactone **87** in high yield and selectivity. Prochiral diol **88** however was unsuccessful in forming enantioenriched lactone **89**. Both lactones contain an all-carbon quaternary center that would be difficult to install otherwise. More detail on desymmetrizations can be found in the paper by Wilent and Petersen.[7]

The kinetic resolution developed was also able to be used on synthetically useful scales. The test substrate used in optimization was shown to have an isolated yield of recovered starting material of 34% and an enantiomeric excess of 93%. The α,α-disubstituted substrate was shown to have an isolated yield of 38% and an enantiomeric excess of 94%.

The final item tested was the utilization of the enantiopure substrate **73a** (figure **27**). Enantiopure hydroxy ester **73a** was transformed into lactone **74a**

using trifluoroacetic acid in dichloromethane with a yield of 92% and no loss of ee. Substrate **73a** was transformed into the amine ester **90** via pyridinium chlorochromate (PCC) oxidation, benzyl amine amination, and sodium triacetoxyborohydride reduction. Amino ester **90** was then transformed into the lactam **91** using trifluoroacetic acid at reflux. Both transformations afforded the product in decent yield with minimal loss of ee. **73a** was reacted with PCC and then Oxone® to yield acid ester **92**. **73a** was also reacted with lithium aluminum hydride to reduce the ester and afford diol **93**. This work was completed by Ghassan Qabaja.

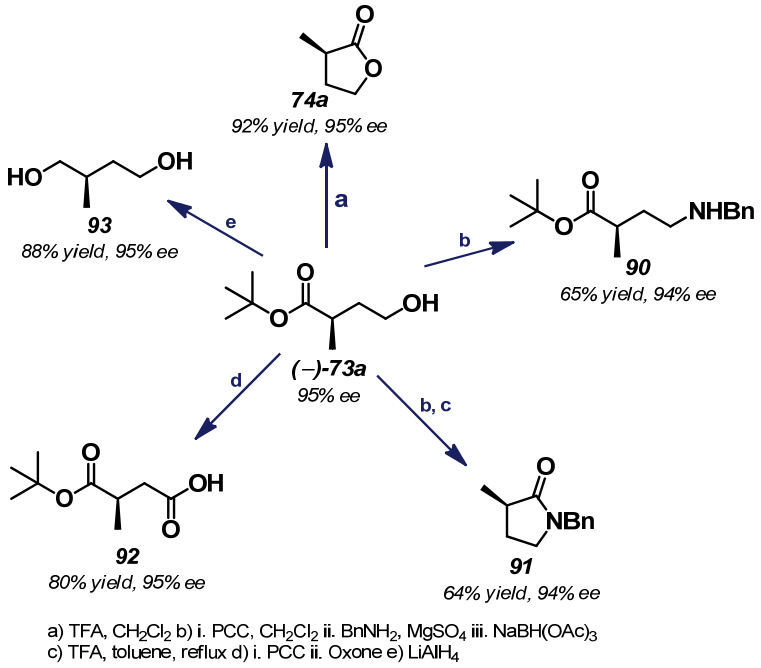


Figure 27. Enantioenriched Building Blocks

2.3 Conclusion

In summary, a facile, enantioselective synthesis of α-substituted γ-hydroxy *tert*-butyl esters via a Brønsted acid catalyzed kinetic resolution has been completed. This work has yielded optimized conditions for the kinetic resolution as well as two highly selective substrates. α-Methyl-γ-hydroxy *tert*-butyl ester has been shown to react to form at least five different compounds while the α-methyl-α-phenyl γ-hydroxy *tert*-butyl ester has a quaternary center that is difficult to form. The optimized conditions from this work will be used in future endeavors as a starting place for other Brønsted acid catalyzed kinetic resolutions in the Petersen lab.

2.4 References

1. a) Johnson, J. A.; Li, N.; Sames, D., Total Synthesis of (—)-Rhazinilam: Asymmetric C-H Bond Activation via the Use of a Chiral Auxiliary. *J. Am. Chem. Soc.* **2002,** *124*, 6900; b) Blaser, H. U., The chiral pool as a source of enantioselective catalysts and auxiliaries. *Chem. Rev.* **1992,** *92*, 935.

2. a) Stewart, J., Dehydrogenases and transaminases in asymmetric synthesis. *Curr. Opin. Chem. Biol.* **2001,** *5*, 120; b) Mischitz, M.; Kroutil, W.; Wandel, U.; Faber, K., Asymmetric microbial hydrolysis of epoxides. *Tetrahedron: Asymmetry* **1995,** *6*, 1261; c) Green, B. S.; Lahav, M.; Rabinovich, D., Asymmetric synthesis via reactions in chiral crystals. *Acc. Chem. Res.* **1979,** *12*, 191.

3. Steven, A.; Overman, L. E., Total Synthesis of Complex Cyclotryptamine Alkaloids: Stereocontrolled Construction of Quaternary Carbon Stereocenters. *Angew. Chem. Int. Ed.* **2007,** *46*, 5488.

4. Chatterjee, I.; Jana, C. K.; Steinmetz, M.; Grimme, S.; Studer, A., Copper-Catalyzed Enantioselective [2+2] Cycloadditions of 2-Nitrosopyridine with Ketenes. *Adv. Synth. Catal.* **2010,** *352*, 945.

5. Paras, N. A.; MacMillan, D. W. C., New Strategies in Organic Catalysis: The First Enantioselective Organocatalytic Friedal-Crafts Alkylation. *J. Am. Chem. Soc.* **2001,** *123*, 4370.

6. Neises, B.; Steglich, W., Simple Method for the Esterification of Carboxylic Acids. *Angew. Chem. Int. Ed.* **1978,** *17*, 522.

7. Wilent, J. E.; Petersen, K. S., Enantioselective Desymmetrization of Diesters. *J. Org. Chem.* **2014,** *79*, 2303.

CHAPTER III

DEVELOPMENT OF A BRØNSTED ACID CATALYZED KINETIC RESOLUTION OF γ-SUBSTITUTED, DISUBSTITUTED, AND CYCLIC HYDROXY ESTERS

3.1 Background

Natural products extracted from animals and plants are found in enantiomerically pure form while the synthetic clones are usually prepared in a 1:1 ratio of enantiomers. In some cases, one enantiomer is harmless while in others one enantiomer provides negative effects. However, even if one enantiomer is harmless, it constitutes waste and a potential pollutant. Consequently, enantiomerically pure compounds are of vital importance to the pharmaceutical fields and asymmetric synthesis of these drugs is a field that has been growing over the last few decades[1]. Single enantiomer pharmaceuticals made up 37% of the total pharmaceutical market sales in 2005[2]. Between 2000 and 2005, single enantiomer compounds annual growth rate increased by 11%.

As seen in chapter 2, kinetic resolutions are still a valid option in asymmetric synthesis. In chapter 3, kinetic resolution of small molecules with multiple stereocenters using a Brønsted acid catalyst is performed. Enantioenriched small building blocks with multiple substituents give the possibility of more handles to manipulate to look like natural products.

Particularly α,γ-disubstituted hydroxy compounds and γ-lactones have the potential to be used in the synthesis of complex macrolides such as the geodiamolide[3] family and the amphidinolide[4] family as well as the compound jaspamide[5] (figure **28**). Bicyclic precursors and lactones also have the potential to be used in natural product synthesis such as antifungals[6] and GABA inhibitors[7] (figure **28**). Cyclic hydroxy ester (–)-**96** and bicyclic lactone (–)-**97** have been used as building blocks for the angiotensine converting enzyme (ACE) inhibitor Trandolapril[8] marketed by Abbott Laboratories.

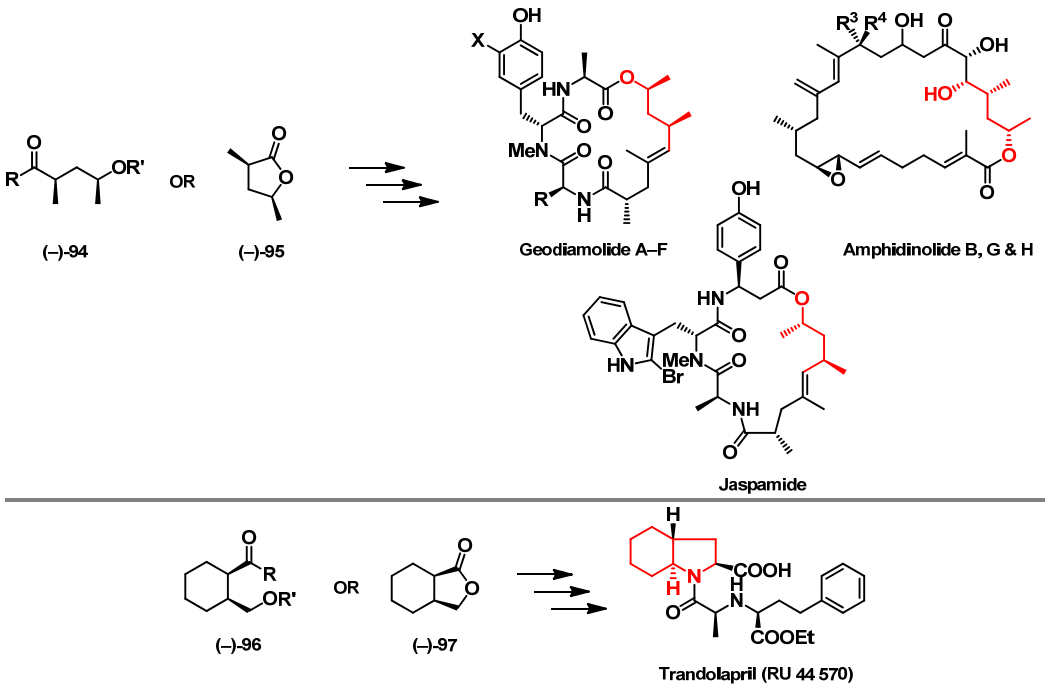


Figure 28. Natural Product Syntheses from Building Blocks with Multiple Stereocenters

3.2 Results and Discussion

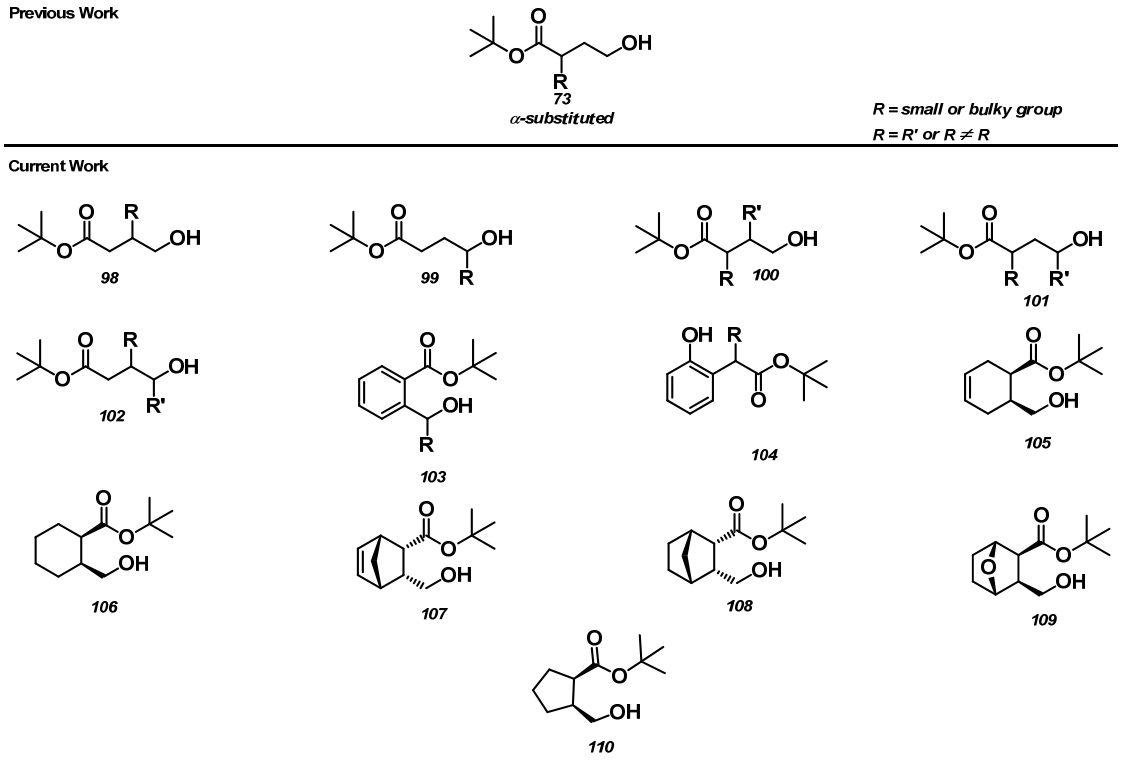


Figure 29. New Substrates

Previously, the Petersen group published an article in *Organic Letters* detailing the kinetic resolution of α-substituted γ-hydroxy *tert*-butyl esters[9]. With the optimized conditions determined, differently functionalized γ-hydroxy *tert*-butyl esters were tested to increase the substrate scope of the previous results. The first to be tested were β- and γ-substituted γ-hydroxy *tert*-butyl esters. To form β-substituted substrate **98**, methyl succinate anhydride was reacted with *tert*-butanol at 60 ˚C overnight (figure **29**). The resulting reaction did not yield desired product so the temperature was increased to 85 ˚C. After a few hours

and no desired product, catalyst *para*-toluenesulfonic acid was added. This reaction was tried for an additional time with *tert*-butanol, dimethylaminopyridine (DMAP), pyridine, and dichloromethane. No desired product was recovered. Jakobsche and group previously showed that propionic acid can be reacted with *tert*-butyl bromoacetate to yield an ester/acid intermediate that could be reduced to the hydroxy ester (figure **30**)[10]. In this experiment, however, very little desired product was obtained from this reaction.

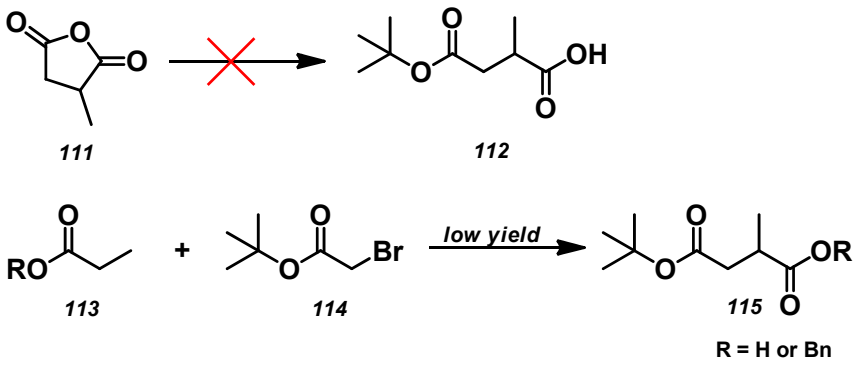


Figure 30. Formation of β-Substituted Hydroxy Esters

γ-Substrates were developed concomitantly with the β-substrates. To form the desired γ-substrates (figure **31**), succinic anhydride (**116**) was simultaneously opened and esterified using DMAP, *N*-hydroxysuccinimide, *tert*-butyl alcohol, and triethylamine (TEA) in toluene at reflux. The carboxylic acid portion of the resulting intermediate (**117**) was then reduced by BH_3•THF and oxidized by pyridinium dichromate (PDC) to the aldehyde (**119**). Phenylmagnesium bromide

or methylmagnesium iodide was reacted with the aldehyde in a Grignard reaction to yield the appropriate γ-substituted hydroxy ester.

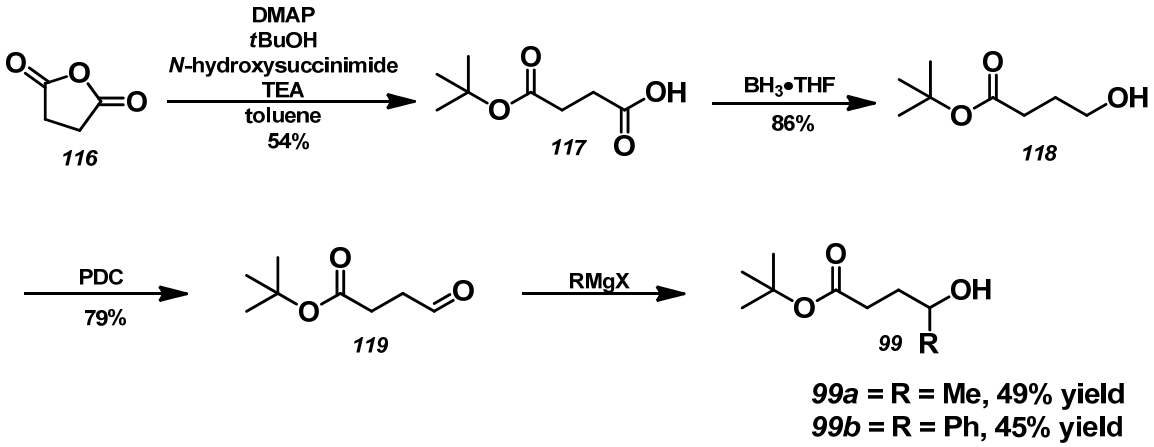
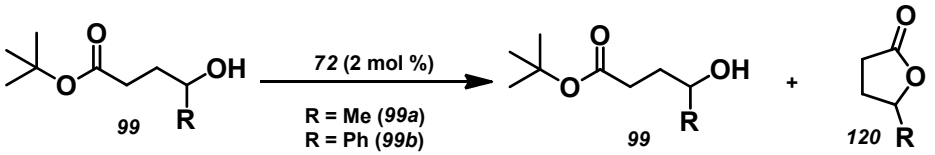
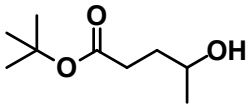
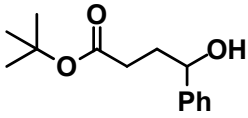


Figure 31. Formation of γ-Substrates

These substrates were able to be produced in reasonable yields with enough material for initial experiments. Both γ-substrates had poor selectivity in the kinetic resolution using our standard conditions developed for α-substitituted hydroxy esters (table **4**).

Table 4. Lactonization of γ-Substrates



Entry	Substrate	Temp (°C)	Time (h)	%conv	%ee$_{sm}$	%ee$_{p}$	s
1		5	24	68	25	2	1.6
2		5	96	51	10	N/A	1.3

The next set of substrates tested was the disubstituted γ-hydroxy *tert*-butyl esters. α,γ-Dimethyl γ-hydroxy *tert*-butyl ester (figure **32**) was formed from the reaction of *tert*-butyl propionate and propylene oxide. To do this, the propionate was first deprotonated at the α-carbon by lithium diisopropylamide (LDA) that was made in situ. Diethyl aluminum chloride and propylene oxide were then added to afford α,γ-dimethyl substrate **101a**.

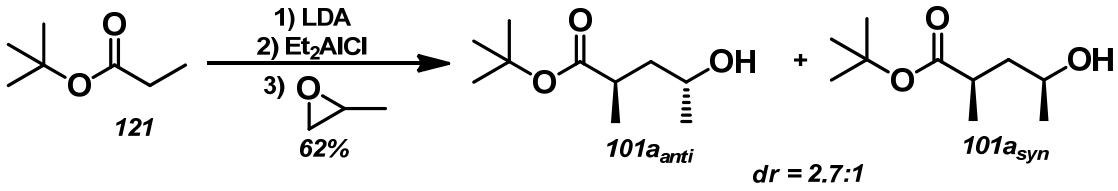


Figure 32. Formation of α,γ-Dimethyl Substrate

The α-methyl-γ-phenyl substrate was planned to be synthesized in the same fashion using styrene oxide. After the analogous reaction was completed,

analysis by NMR indicated that the phenyl ring was placed on the β-carbon (figure **33**) due to the nucleophile attacking the secondary carbon forming **100a**. α-Methyl-γ-phenyl γ-hydroxy *tert*-butyl ester **101b** was then formed from commercially available 2-methyl-4-oxo-4-phenyl butyric acid (**122**). Acid **122** was esterified via Steglich esterification using DCC and DMAP. The ketone/ester **123** was then reduced using sodium borohydride ($NaBH_4$) to yield the hydroxy ester **101b**.

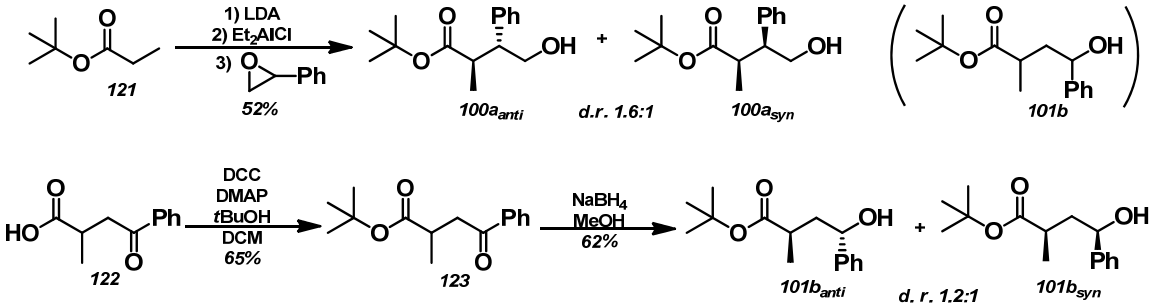
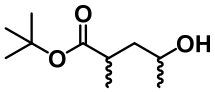
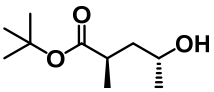
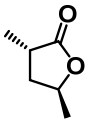
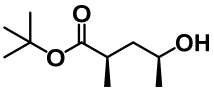
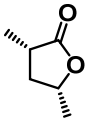
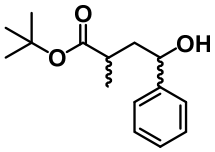
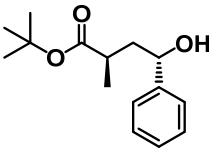
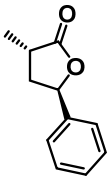
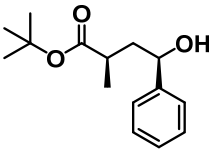
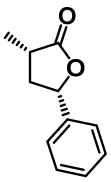
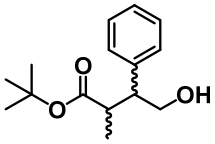
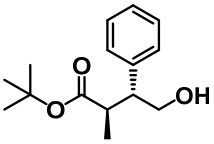
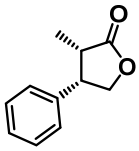
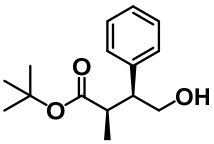
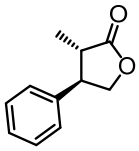
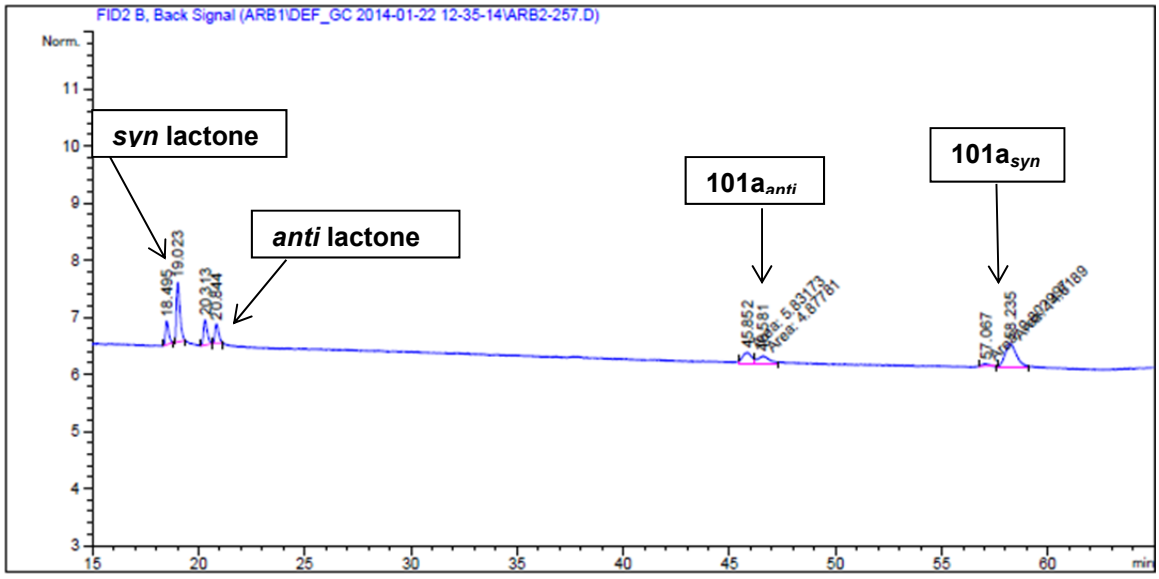


Figure 33. Formation of α-Methyl-β-phenyl and α-Methyl-γ-phenyl Substrates

These disubstituted hydroxy esters underwent kinetic resolution as diastereomeric mixtures as it was difficult to separate the diastereomers by any means. The lactonization of the disubstituted hydroxy esters was executed in dichloromethane at the given temperature and time with catalyst **72**. As seen in table **5**, most lactonizations did not yield high selectivities of either product or recovered starting material. Substrate **101a*syn*** was the only hydroxy ester in the set to show high selectivity.

Table 5. Results of the Kinetic Resolution of Disubstituted Hydroxy Esters

Entry	Substrate	Enantioenriched Hydroxy Ester	Enantioenriched Lactone	Temp (°C)	Time (h)	% conv	% ee_{sm}	% ee_P	s
101a$_{anti}$				-5	48	70	21	1	1.4
101a$_{syn}$				-5	24	44	62	13	15.8
101b$_{anti}$				5	96	91	10	13	1.1
101b$_{syn}$				5	96	58	15	21	1.4
100a$_{anti}$				-5	20	74	50	8	2.2
100a$_{syn}$				-5	20	44	10	3	1.4

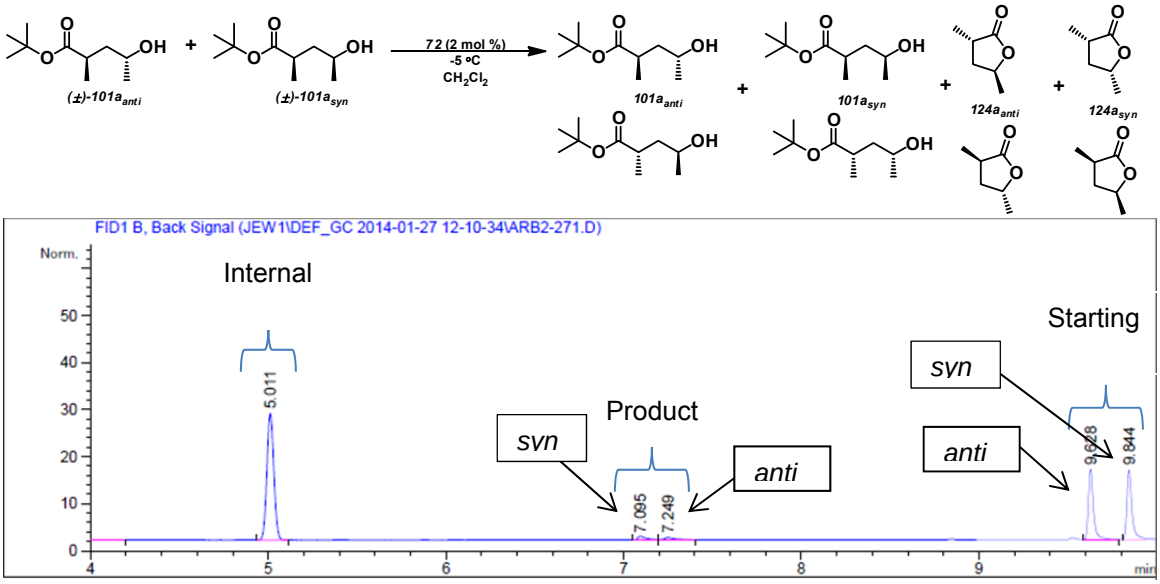


	Peak 1 area	Peak 2 area	% ee
***Syn* Lactone**	7.78319	18.95474	42
***Anti* Lactone**	15.81304	12.93517	10
***Anti* Hydroxy Ester**	11.14236	8.98100	11
***Syn* Hydroxy Ester**	1.04258	23.34792	91

Figure 34. Chiral GC Chromatogram Displaying ee's of Compound 100a

However, with 8 possible compounds, the conversion for lactonization needs to be calculated carefully. In this case, an internal standard was used for the lactonization of diastereomers. The internal standard, xylene, was chosen from a group of non-polar compounds by establishing the retention time on GC. A non-polar, non-reacting compound is needed so that there is no interference during lactonization. To perform the reaction, a stock solution of xylene in dichloromethane (226 mg in 500 mL) was prepared. The chosen substrate would

then be dissolved in dichloromethane (10 mg in 10 mL) and 1 mL of the stock solution. An initial time point was taken before catalyst was added. This was done to determine the response factor, a number that accounts for differences in response between the analyte and internal standard.



Peak Name	Retention Time (min)
Xylene	5.011
***Syn* Lactone**	7.095
***Anti* Lactone**	7.249
***Anti* Hydroxy Ester**	9.628
***Syn* Hydroxy Ester**	9.844

Figure 35. Chromatogram of t_0

The first calculation involves t_0. This is to find the **internal response factor** (IRF).

$$\frac{area_{is} \times amount_s}{amount_{is} \times area_s} = IRF$$

Where *is* = internal standard and *s* = substrate. The amounts must be exact and in mg form. The response factor is used to determine the amount of the substrate at t_1 and on. In the case above, the area of the internal standard was 0.03660, the area of **101a**$_{anti}$ was 0.01464, and the area of **101a**$_{syn}$ was 0.01488. The ratio of *anti* to *syn* was 0.98:1. The ratio needs to be considered to determine the amount of each isomer present in solution. An IRF is then calculated for each hydroxy ester.

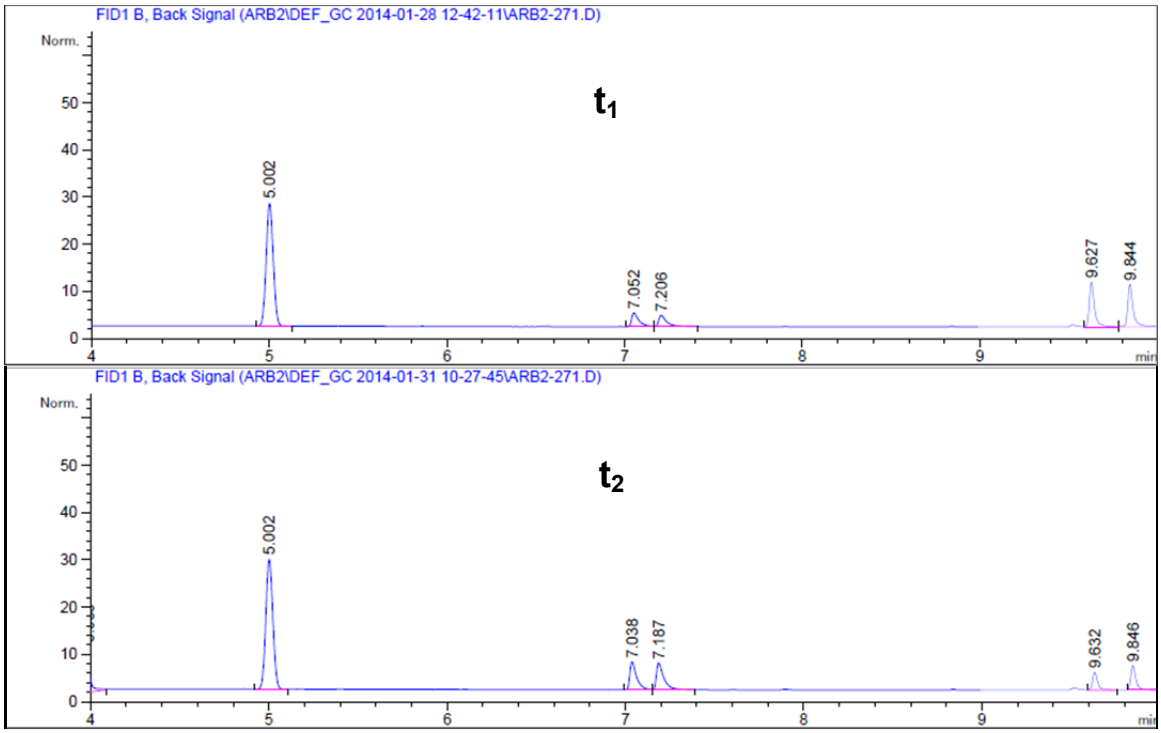


Figure 36. Chromatograms at t_1 and t_2

To determine the amount of substrate after t_0:

$$\frac{amount_{is} \times area_s \times IRF}{area_{is}} = amount_s$$

Again where *is* = internal standard, *s* = substrate, and *IRF* is the response factor previously found.

Table 6. IRF Calculations

	Amount IS	Area IS	Amount of Substrate	Area of Substrate	IRF
***Anti* Hydroxy Ester**	226 mg	0.03660	5.05 mg	0.01488	0.055
***Syn* Hydroxy Ester**	226 mg	0.03660	4.95 mg	0.01464	0.055

Table 7. Conversion Calculations Based on IRF Values

	IRF	Amount IS	Area IS	Area of Substrate	Amount of Substrate	% conv
t_1	0.055	226 mg	56.63461	15.42653	3.39 mg	32.9%
t_2	0.055	226 mg	6.98968	0.95325	1.70 mg	66.3%
t_1	0.055	226 mg	56.63461	15.33903	3.37 mg	31.9%
t_2	0.055	226 mg	6.98968	0.69510	1.27 mg	74.3%

Due to the lack of separation of diastereomers and the fact that substrate **101a**$_{syn}$ was not formed in high diastereomeric excess, another method for this diastereoselective formation was explored. In the new method, 2-

(bromomethyl)acrylic acid (**125**) was reacted with acetaldehyde and indium in tetrahydrofuran at room temperature (figure **37**)[11]. The resulting lactone (**127**) was hydrogenated to yield α,γ-dimethyl lactone **128**. The lactone was checked by achiral GC to determine if the *syn* configuration was the sole product. Upon determination, the lactone was opened through a reaction with first benzylbromide and potassium hydroxide in toluene then potassium hydroxide in methanol and water. The ether/acid **129** was then esterified with di-*tert*-butyl dicarbonate, *N,N*-dimethylaminopyridine, and *tert*-butyl alcohol in dichloromethane. The resulting ester **130** was deprotected through hydrogenolysis to remove the benzyl group and yield hydroxy ester **101a**$_{syn}$.

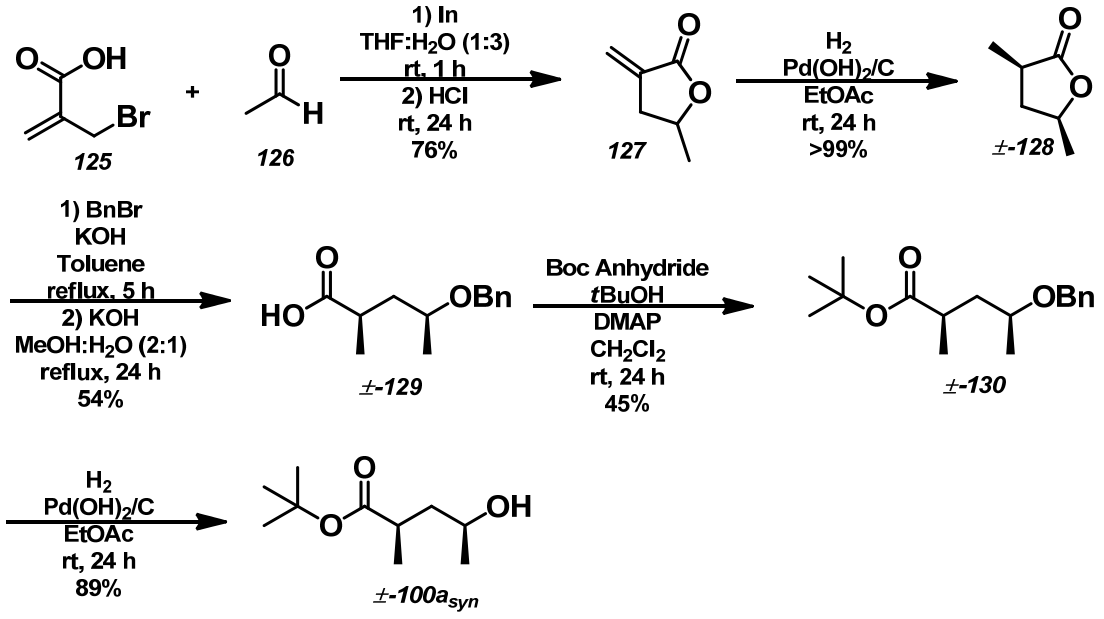


Figure 37. Formation of *Syn*-α,γ-Dimethyl Hydroxy Ester

Hydroxy ester **101a$_{syn}$** was lactonized on a large scale in dichloromethane at -5 ˚C with a catalyst load of 2 mol %. This reaction yielded 31% of enantioenriched hydroxy ester (99% ee, s = 15.7). The enriched hydroxy ester was lactonized with *p*-toluenesulfonic acid to yield enantioenriched lactone. Compared to literature values for optical rotation, the absolute configuration of the hydroxy ester was found to be *R,S*-α,γ-dimethyl hydroxy *tert*-butyl ester.

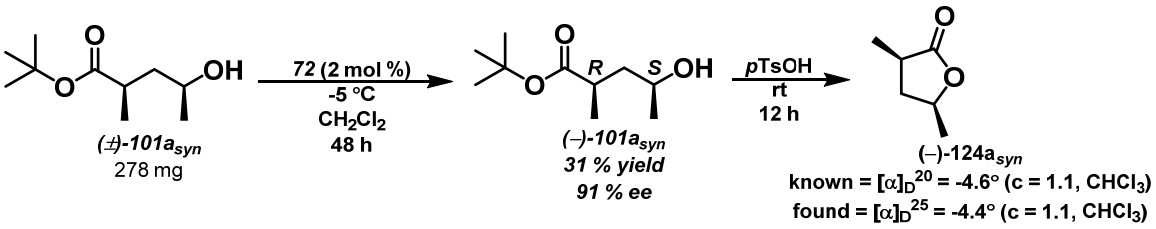
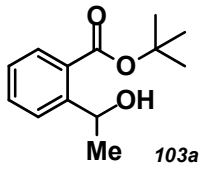
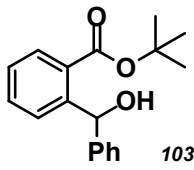
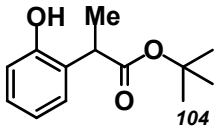
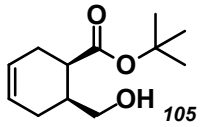
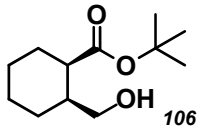
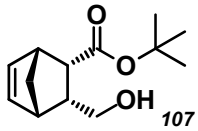
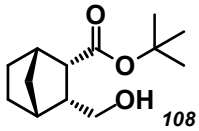
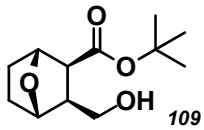
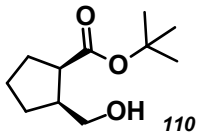


Figure 38. Large Scale Lactonization of 100a$_{syn}$

Ghassan Qabaja, a post-doc in the Petersen lab, has been working on the bicyclic precursors and lactones (substrates **103**-**110**, figure **29**). Dr. Qabaja is still currently working on this project. His current results are listed in table **8**.

Table 8. Lactonization of Cyclic Hydroxy Esters

Entry	Substrate	Temp (°C)	Time (h)	% conv	%ee_{sm}	%ee_p	s
1	 *103a*	-20	48	76	57	8	2.3
2	 *103b*	5	96	68	26	5	1.6
3	 *104*	RT	120	N/A	22	25	N/A
4	 *105*	-20	64	56	80	35	10.4
5	 *106*	0	20	60	≥95	33	15.7
6	 *107*	5	48	58	75	8	7.3
7	 *108*	-5	70	N/A	17	49	N/A
8	 *109*	-20	12	62	94	55	12.4
9	 *110*	-20	24	49	41	53	3.6

3.3 Conclusion

In summary, the Brønsted acid catalyzed kinetic resolution of γ-substituted and disubstituted hydroxy esters has been shown. It was seen that most of the substrates were not enantioenriched under the current conditions. In the future, different Brønsted acid catalysts could be used to optimize these conditions and yield enantioenriched material. The cyclic hydroxy esters have shown more promising results; however, it is still in preliminary stages and the reactions need to be optimized before further experiments can be conducted.

3.4 References

1. Caner, H.; Groner, E.; Levy, L., Trends in the development of chiral drugs. *Drug Discovery Today* **2004,** *9*, 105.

2. Erb, S. Single-Enantiomer Drugs Poised for Further Market Growth.

3. a) Hirai, Y.; Yokota, K.; Sakai, H.; Yamazaki, T.; Momose, T., A Total Synthesis of the Novel Cyclodepsipeptide (+)-Geodiamolide A. *Heterocycles* **1989,** *29*, 1865; b) Hirai, Y.; Yokota, K.; Yamazaki, T.; Momose, T., A Total Synthesis of (+)-Geodiamolides A and B, the Novel Cyclodepsipeptides. *Heterocycles* **1990,** *30*, 1101; c) White, J. D.; Amedio, J. C., Total Synthesis of Geodiamolide A, a Novel Cyclodepsipeptide of Marine Origin. *J. Org. Chem.* **1989,** *54*, 736.

4. a) Hara, A.; Morimoto, R.; Iwasaki, Y.; Saitoh, T.; Ishikawa, Y.; Nishiyama, S., Total Syntheses of Amphidinolides B, G, and H. *Angew. Chem. Int. Ed.* **2012,** *51*, 9877; b) Lu, L.; Zhang, W.; Nam, S.; Horne, D. A.; Jove, R.; Carter, R. G., Amphidinolide B: Total Synthesis, Structural Investigation, and Biological Evaluation. *J. Org. Chem.* **2013,** *78*, 2213.

5. a) Chiarello, J.; Joullié, M. M., Synthesis of the C_5-C_9 Fragment of the Polypropionate Unit of the Geodiamolides and Jaspamide. *Synthetic Comm.* **1989,** *19*, 3379; b) Kang, S. K.; Lee, D. H., Stereocontrolled Synthesis of the

Non-Peptide C1-C9 Segment of Jaspamide and Geodiamolides. *Synlett* **1991**, 175.

6. Olejniczak, T.; Boratyński, F.; Bialońska, A., Fungistatic Activity of Bicyclo[4.3.0]-γ-lactones. *J. Agric. Food. Chem.* **2011,** *59*, 6071.

7. Baxendale, I. R.; Ernst, M.; Krahnert, W. R.; Ley, S. V., Application of Polymer-Supported Enzymes and Reagents in the Synthesis of gamma-Aminobutyric Acid (GABA) Analogues. *Synlett* **2002**, 1641.

8. Brion, F.; Marie, C.; Mackiewicz, P.; Roul, J. M.; Buendia, J., Stereoselective Synthesis of a trans-Octahydroindole Derivative, Precursor of Trandolapril (RU 44 570), and Inhibitor of Angiotensin Converting Enzyme. *Tetrahedron Lett.* **1992,** *33*, 4889.

9. Qabaja, G.; Wilent, J. E.; Benavides, A. R.; Bullard, G. E.; Petersen, K. S., Facile Synthesis of Versatile Enantioenriched α-Substituted Hydroxy Esters through a Brønsted Acid Catalyzed Kinetic Resolution. *Org. Lett.* **2013,** *15*, 1266.

10. a) Jakobsche, C. E.; Peris, G.; Miller, S. J., Functional Analysis of an Aspartate-Based Epoxidation Catalyst with Amide-to-Alkene Peptidomimetic Catalyst Analogues. *Angew. Chem. Int. Ed.* **2008,** *47*, 6707; b) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S., A General Method for the Synthesis of Enantiomerically Pure ß-Substituted, ß-Amino Acids through α-Substituted Succinic Acid Derivatives. *J. Org. Chem.* **1999,** *64*, 6411; c) Davies, S. G.; Dixon, D. J., Asymmetric syntheses of moiramide B and andrimid. *J. Chem. Soc., Perkins Trans. 1* **1998**, 2635.

11. Feng, J. T.; Wang, D. L.; Wu, Y. L.; He, Y.; Xing, Z., New antifungal scaffold derived from a natural pharmacophore: Synthesis of α-methylene-Γ-butyrolactone derivatives and their antifungal activity against Colletotrichum lagenarium. *Bioorg. Med. Chem. Lett.* **2013,** *23*, 4393.

CHAPTER IV

EXPERIMENTAL

4.1 General Information

All anhydrous reactions were performed with dry solvents in oven dried glassware under an argon atmosphere. Unless otherwise noted, all solvents and reagents were obtained from commercial sources and used without further purification. Purification via column chromatography was performed using silica gel (60 Å, 32-63 μm). NMR spectra were recorded using a JEOL ECA spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Coupling constants, *J*, are reported in hertz (Hz) and multiplicities are listed as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of triplets (tt), multiplet (m), etc. IR data was obtained with a Perkin Elmer FTIR spectrometer with frequencies reported in cm^{-1}. High Resolution Mass Spectra were acquired on a ThermoFisher Scientific LTQ Orbitrap XL MS system.

4.2 Benzyl Ether 76

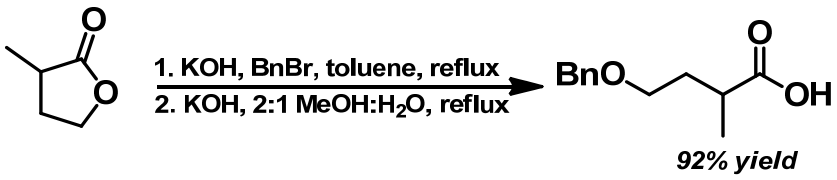


Figure 39. Benzyl Ether 76

Crushed KOH (3.0 g, 53.0 mmol) was added to a toluene (18 mL) solution of α-methyl-γ-butyrolactone (1.0 g, 10 mmol) and benzyl bromide (7.0 g, 40 mmol). The reaction mixture was stirred at 110 ˚C for 5 h and then toluene was removed in vacuo. Next, methanol (20 mL) was added to reaction flask followed by crushed KOH (1.0 g, 17 mmol) and water (10 mL) then the reaction mixture was refluxed for 16 h. The reaction mixture was extracted with diethyl ether (3 x 20 mL), the aqueous layer was acidified with concentrated HCl, and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Mg_2SO_4, filtered, and concentrated in vacuo to give the product as a pale yellow oil (1.9 g, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.40 (m, 5H), 4.50 (m, 2H), 3.52 (t, *J*=5 Hz, 2H), 2.7 (m, 1H), 2.05 (m, 1H), 1.70 (m, 1H), 1.20 (d, *J*=5 Hz, 3H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 182.50, 138.30, 128.47, 127.73, 127.70, 73.07, 67.89, 36.53, 33.29, 17.10 ppm

IR (neat) 3030, 2936, 2864, 1701, 1496, 1454, 1414, 1364, 1288, 1242, 1204, 1094, 1026, 941 cm^{-1}

HRMS (ESI) $C_{12}H_{16}O_3$ $[M+H]^{+1}$, calculated 209.1133, found 209.1162

4.3 Intermediate 77

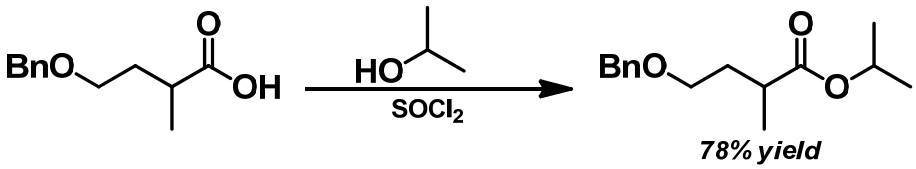


Figure 40. Intermediate 77

The carboxylic acid/ether (0.25 g, 1.2 mmol) was dissolved in isopropanol (0.75 mL, 9.8 mmol). Thionyl chloride (0.12 mL, 1.7 mmol) was added dropwise to the solution at room temperature. The reaction mixture was refluxed for 4 h. The solution was neutralized with $NaHCO_3$ and extracted with diethyl ether (3 x 2 mL). The combined organic layers were dried over Mg_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (10% EtOAc in hexanes) afforded the intermediate ester/benzyl ether as a colorless oil (234 mg, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.98 (m, 1H), 4.48 (s, 2H), 3.48 (m, 2H), 2.58 (m, 1H), 2.00 (m, 1H), 1.70 (m, 1H), 1.20 (d, *J* = 5.16 Hz, 3H), 1.19 (d, *J* = 4.58, 3H), 1.14 (d, *J*=6.87 Hz, 3H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.13, 138.81, 128.65, 127.94, 127.65, 72.93, 67.85, 67.15, 36.31, 33.16, 21.94, 17.38 ppm

IR (neat) 2979, 2361, 1725, 1454, 1373, 1179, 1104, 734, 696, 507 cm^{-1}

HRMS (ESI) $C_{15}H_{22}O_3$ $[M+H]^{+1}$, calculated 251.1672, found 251.1637

4.4 Hydroxy Isopropyl Ester 73b

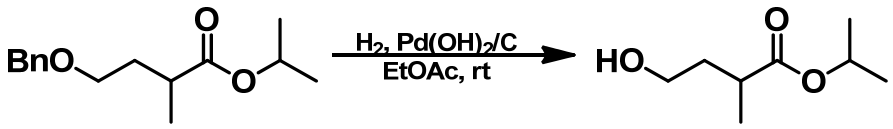


Figure 41. Hydroxy Isopropyl Ester 73b

To the above intermediate (0.204 g, 1.3 mmol) in EtOAc (8 mL) was added $Pd(OH)_2/C$ (0.02 g, 10% by weight of intermediate). The reaction flask was flushed of all gases then a balloon of H_2 was added to the flask. The reaction stirred overnight at room temperature. The mixture was filtered through a plug of Celite® and the filtrate was concentrated. The concentrated filtrate was purified using flash chromatography on silica gel (1→5% acetone in CH_2Cl_2). The fractions were check by GC to detect product. No yield was obtained on this compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (m, 1H), 3.68 (td, *J*=6.16, 4.87 Hz, 2H), 2.59 (dd, *J*=8.31, 1.43 Hz, 1H) 1.91 (m, 1H), 1.69 (m, 1H), 1.23 (d, *J* = 2.86, 3H), 1.21 (d, *J* = 2.86, 3H), 1.19 (m, 3H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.54, 67.78, 60.80, 36.81, 36.38, 21.87, 17.29 ppm

IR (neat) 3416, 2979, 2361, 1725, 1456, 1374, 1176, 1121, 1049, 519, 509 cm^{-1}

HRMS (ESI) $C_8H_{16}O_3$ $[M+H]^{+1}$, calculated 161.1172, found 161.1167

4.5 Intermediate 85

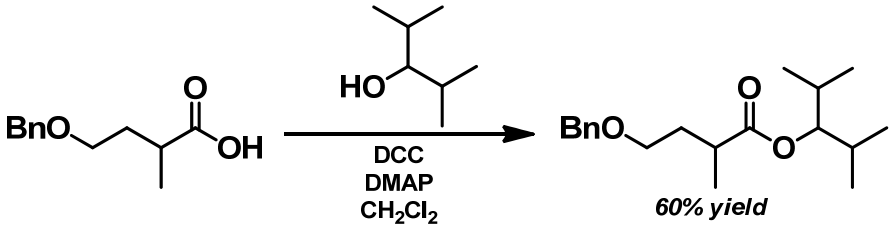


Figure 42. Intermediate 85

DCC (1.25 g, 6 mmol) was added to a mixture of the carboxylic acid/ether (1.04 g, 5.0 mmol), DMAP (0.125 g, 1 mmol), 2,4-dimethyl-3-pentanol (21 mL, 15 mmol), and CH_2Cl_2 (50 mL) at room temperature. The reaction mixture was stirred at -10 ˚C for 24 h. The mixture was diluted with hexanes (50 mL), filtered, and concentrated in vacuo. Flash chromatography on silica gel (5% EtOAc in hexanes) afforded the intermediate as a clear and colorless oil (1.35 g, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.59 (m, 1H), 4.48 (m, 2H), 3.51 (qt, *J*= 9,69, 6.37 Hz, 2H), 2.69 (m, 1H), 2.07 (m, 1H), 1.88 (qd, *J*= 6.68, 5.16 Hz, 2H), 1.70 (m, 1H), 1.20 (d, *J*= 7.45 Hz, 3H) 0.85 (m, 12H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.54, 138.47, 128.48, 127.80, 127.68, 82.30, 73.12, 68.14, 36.93, 33.54, 29.49, 19.71, 17.38 ppm

IR (neat) 2968, 2360, 1727, 1454, 1368, 1177, 1096, 950, 733, 696, 506 cm^{-1}

HRMS (ESI) $C_{19}H_{30}O_3$ $[M+H]^{+1}$, calculated 307.2272, found 307.2257

4.6 Hydroxy Dimethylpentyl Ester 73c

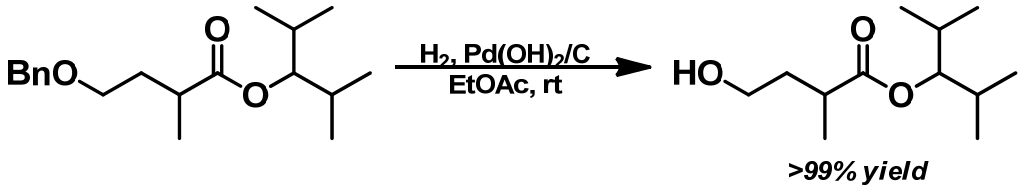


Figure 43. Hydroxy Dimethylpentyl Ester 73c

To the above intermediate (1.35 g, 4.41 mmol) in EtOAc (45 mL) was added $Pd(OH)_2/C$ (0.14 g, 10% by weight of intermediate) was added. The reaction flask was flushed of all gases and then a balloon of H_2 was added to the flask. The reaction was stirred overnight at room temperature. The mixture was filtered through a pad of Celite ® and concentrated in vacuo to afford compound as a colorless oil (0.97 g, >99% yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (t, *J*= 6.01 Hz, 1H), 3.69 (td, *J*=6.30, 2.29 Hz, 2H), 2.67 (dt, *J*= 7.88, 6.66 Hz, 1H), 1.97 (m, 1H), 1.89 (ddd, *J*= 13.17, 6.59, 3.72 Hz, 2H) 1.69 (m, 1H), 1.23 (m, 3H), 0.86 (m, 12H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.93, 82.64, 60.85, 37.07, 36.30, 29.46, 19.67, 17.40 ppm

IR (neat) 3447, 2969, 2360, 1728, 1462, 1387, 1252, 1172, 1129, 1104, 999, 964, 945, 813, 512 cm^{-1}

HRMS (ESI) $C_{12}H_{24}O_3$ $[M+H]^{+1}$, calculated 217.1772, found 217.1792

4.7 4-(*Tert*-butoxy)-4-oxobutanoic Acid 117

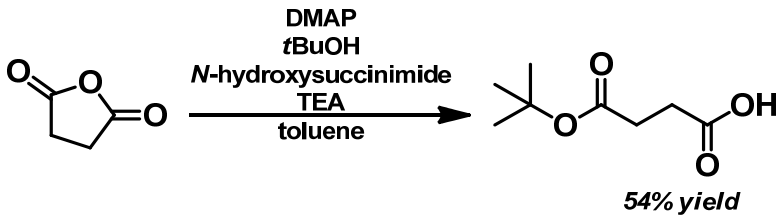


Figure 44. 4-(*Tert*-butoxy)-4-oxobutanoic Acid 117

Succinic anhydride (5 g, 50 mmol), *N*-hydroxysuccinimide (1.73 g, 15 mmol), and DMAP (1.83 g, 15 mmol) were dissolved in toluene (25 mL) at rt. *t*-Butanol (6.22 mL, 65 mmol) and triethylamine (2.09 mL, 15 mmol) were added to the mixture and the reaction was heated at reflux overnight. The reaction mixture was then washed with 10% citric acid (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over Mg_2SO_4, filtered, and concentrated in vacuo yielding pure yellow oil (4.673 g, 54%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 (d, *J* = 6.87 Hz, 2H), 2.53 (d, *J* = 6.87 Hz, 2H), 1.44 (m, 9H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.11, 171.51, 81.12, 30.14, 29.16, 28.09 ppm

IR (neat) 1787, 1712, 1366, 1146, 1069, 845 cm^{-1}

HRMS ($C_8H_{14}O_3$, ESI) $[M-H]^-$, calculated 173.1827, found 173.0811

4.8 *Tert*-butyl 4-Hydroxybutanoate 118

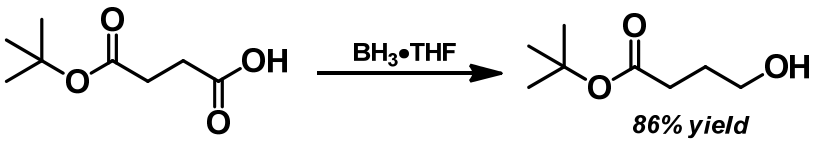


Figure 45. *Tert*-butyl 4-Hydroxybutanoate 118

To a solution of 4-(*tert*-butoxy)-4-oxobutanoic acid (4.673 g, 27 mmol) in dry THF (45 mL) was added BH_3•THF (1M, 30 mL, 30 mmol) dropwise at 0 ˚C. The reaction mixture was stirred overnight at rt. The reaction was cooled to 0 ˚C. DI water (30 mL) and solid K_2CO_3 were added to the reaction mixture. The mixture was then extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over Mg_2SO_4, filtered, and concentrated in vacuo yielding pure yellow oil (3.705 g, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (m, 2H), 3.44 (m, 2H), 2.15 (m, 2H), 1.27 (m, 9H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 25.67, 28.13, 32.49, 62.19, 80.64, 173.62 ppm

IR (neat) 3384, 2976, 2932, 1726, 1366, 1249, 1147, 1056, 844 cm^{-1}

HRMS (ESI) $C_8H_{14}O_3$ $[M+H-C_4H_8]^+$ calculated 105.1073, found 105.0549

4.9 *Tert*-butyl 4-Oxobutanoate 119

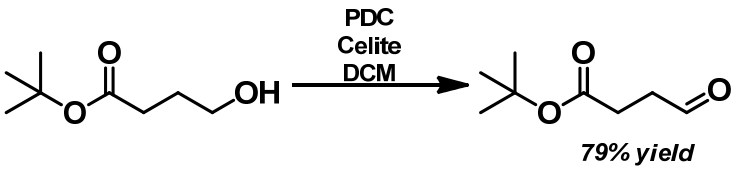


Figure 46. *Tert*-butyl 4-Oxobutanoate 119

A flame-dried round bottom flask was flushed with argon. Pyridinium dichromate (5.267 g, 14 mmol) and celite (5.267 g) were then placed in the flask, air was evacuated and argon was flushed in. $CHCl_2$ (80 mL) was added to the system and then *tert*-butyl 4-hydroxybutanoate (1.73 g, 10.8 mmol) dissolved in $CHCl_2$ (20 mL) was added to the flask. The reaction mixture stirred at rt overnight. The mixture was then filtered through celite and concentrated in vacuo. Purification was done via column chromatography (1.5" x 7" silica gel, 20% Et_2O in pet. ether) which yielded 1.341 g of yellow oil product (79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 2.72 (m, 2H), 2.54 (m, 2H), 1.43 (s, 9H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.55, 171.61, 81.02, 38.81, 28.11, 27.94 ppm

IR (neat) 2978, 2935, 2828, 2729, 1721, 1366, 1241, 1148, 844 cm^{-1}

4.10 *Tert*-butyl 4-Hydroxypentanoate 99a

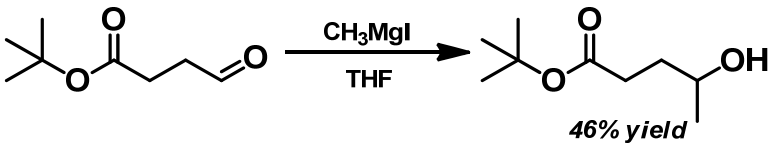


Figure 47. *Tert*-butyl 4-Hydroxypentanoate 99a

119 (0.095 g, 0.6 mmol) in THF (4 mL) was placed in a flame-dried round bottom flask under argon at -78 ˚C. Methylmagnesium bromide (3M in THF, 0.23 mL, 0.7 mmol) was added dropwise and the reaction mixture stirred at -78 ˚C for 5 hours. The reaction was quenched with NH_4Cl, extracted with EtOAc, dried, and concentrated in vacuo. Purification was done by column chromatography (0.5" x 5.5" silica gel, 20% EtOAc in Hexanes) yielding 0.048 g of yellow oil product (46%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (m, 1H), 2.34 (t, *J* = 7.16 Hz, 2H), 1.71 (m, 2H), 1.43 (s, 9H), 1.19 (d, *J* = 6.30 Hz, 3H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.72, 80.58, 67.57, 34.05, 23.59, 32.16, 28.15 ppm

IR (neat) 3424, 2967, 2931, 1729, 1456, 1366, 1256, 1150, 1079, 943, 845 cm^{-1}

HRMS (ESI): $C_9H_{18}O_3$ $[M+H]^{+1}$, calculated 175.2473, found 175.0759

4.11 *Tert*-butyl 4-Hydroxy-4-(4-methoxyphenyl)butanoate 99b

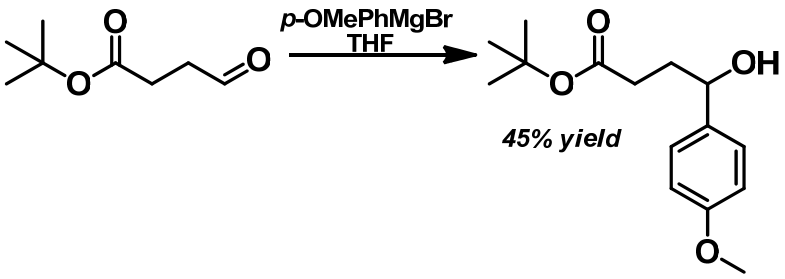


Figure 48. *Tert*-butyl 4-Hydroxy-4-(4-methoxyphenyl)butanoate 99b

119 (0.569 g, 3.6 mmol) in THF (24 mL) was placed in a flame-dried round bottom flask under argon at -78 ˚C. *P*-methoxyphenylmagnesium bromide (0.5M in THF, 8.6 mL, 4.3 mmol) was added dropwise and the reaction mixture stirred at -78 ˚C for 3 hours. The reaction was quenched with NH_4Cl, extracted with EtOAc, dried and concentrated in vacuo. Purification was done by column chromatography (1" x 7" silica gel, 10-20% EtOAc in Hexanes) yielded 0.431 g of colorless liquid product (45%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.59 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 4.69 (m, 1H), 3.80 (s, 3H), 2.30 (m, 2H), 2.01 (m, 2H), 1.44 (s, 9H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.45, 159.12, 136.44, 127.10, 113.92, 80.60, 73.43, 55.38, 34.03, 32.11, 28.18 ppm

IR (neat) 3438, 2976, 2932, 2836, 1723, 1611, 1585, 1511, 1456, 1366, 1243, 1145, 1033, 830, 752 cm^{-1}

HRMS (ESI) $C_{15}H_{22}O_4$ $[M+Na]^{+1}$, calculated 289.3191, found 289.1411

4.12 *Tert*-butyl 4-Hydroxy-2-methyl-3-phenylbutanoate 100a

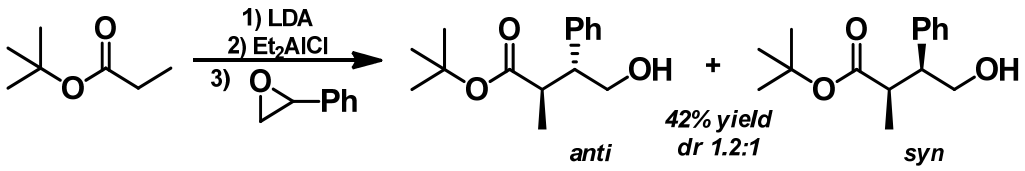


Figure 49. *Tert*-butyl 4-Hydroxy-2-methyl-3-phenylbutanoate 100a

Lithium diisopropylamide was prepared in situ by dissolving distilled diisopropylamine (1.6 mL, 11.4 mmol) in dry THF (15 mL) in a flame-dried flask under argon at -78 ˚C. *n*-Butyllithium (1.6 M in hexanes, 7.1 mL, 11.4 mmol) was added dropwise and the mixture was stirred for 15 min at -78 ˚C. *Tert*-butyl propionate (1.1mL, 7.6 mmol) was then added dropwise and the mixture was stirred for 15 min at -78 ˚C. Diethylaluminum chloride (1M in hexanes, 7.6 mL, 7.6 mmol) was added dropwise and the mixture was stirred for 15 min at -78 ˚C. Styrene oxide (0.43 mL, 3.8 mmol) was added dropwise and the mixture was stirred for 2 hours at -78 ˚C. The reaction was quenched with NH_4Cl and added to a beaker with 4M HCl (20 mL) and ice (10 g). After the ice had melted, the aqueous mixture was extracted twice with ether and the organic layer was washed twice with 5% $NaHCO_3$, once with brined, dried, and concentrated in vacuo. Purification was done by column chromatography (1” x 9” silica gel, 10-20% EtOAc in hexanes) to yield 0.400 g colorless oil mixture of diastereomers (42%, dr 1.2:1).

anti: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.33 (m, 2H), 7.22 (m, 2H), 3.80 (m, 2H), 2.99 (m, 1H), 2.65 (dd, *J* = 10.31, 6.87 Hz, 1H), 1.49 (s, 9H), 0.93 (d, *J* = 6.87 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.78, 140.08, 128.81, 128.69, 127.21, 80.84, 65.91, 51.67, 43.16, 28.21, 16.33

IR (neat) 3423, 2976, 2932, 1722, 1454, 1367, 1246, 1148, 1065, 846, 698 cm^{-1}

syn: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.23 (m, 3H), 3.91 (m, 1H), 3.82 (m, 1H), 2.98 (m, 1H), 2.79 (m, 1H), 1.23 (d, *J* = 6.87 Hz, 3H), 1.18 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.15, 140.58, 128.77, 128.57, 127.18, 80.29, 64.43, 51.26, 42.83, 27.74, 15.59

IR (neat) 3422, 2979, 2938, 1712, 1456, 1368, 1153, 848 cm^{-1}

4.13 *Tert*-butyl 4-Hydroxy-2-methylpentanoate 101a

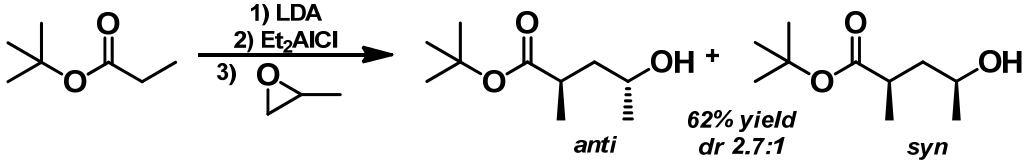


Figure 50. *Tert*-butyl 4-Hydroxy-2-methylpentanoate 101a

Lithium diisopropylamide was prepared in situ by dissolving distilled diisopropylamine (1.6 mL, 11.4 mmol) in dry THF (15 mL) in a flame-dried flask under argon at -78 ˚C. *n*-Butyllithium (1.6 M in hexanes, 7.1 mL, 11.4 mmol) was added dropwise and the mixture was stirred for 15 min at -78 ˚C. *Tert*-butyl propionate (1.1 mL, 7.6 mmol) was then added dropwise and the mixture was

stirred for 15 min at -78 ˚C. Diethylaluminum chloride (1M in hexanes, 7.6 mL, 7.6 mmol) was added dropwise and the mixture was stirred for 15 min at -78 ˚C. Propylene oxide (0.27 mL, 3.8 mmol) was added dropwise and the mixture was stirred for 2 hours at -78 ˚C. The reaction was quenched with NH_4Cl and added to a beaker with 4M HCl (20 mL) and ice (10 g). After the ice had melted, the aqueous mixture was extracted twice with ether and the organic layer was washed twice with 5% $NaHCO_3$, once with brined, dried, and concentrated in vacuo. Purification was done by column chromatography (1" x 9" silica gel, 10-20% EtOAc in hexanes) to yield 0.887 g colorless oil mixture of diastereomers (62%, dr 2.7:1).

anti: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.79 (m, 1H), 2.54 (m, 1H), 1.68 (d, *J* = 3.66 Hz, 1H), 1.46 (dd, *J* = 9.16, 4.58 Hz, 1H), 1.40 (s, 9H), 1.14 (d, *J* = 6.41, 3H), 1.09 (d, *J* = 6.87 Hz, 3H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.52, 80.48, 65.80, 43.18, 37.34, 28.10, 23.69, 17.86 ppm

IR (neat) 3386, 2973, 2934, 1708, 1457, 1367, 1255, 1148, 1081, 1035, 848 cm^{-1}

HRMS (ESI) $C_{10}H_{20}O_3$ $[M+Na]^{+1}$, calculated 211.129, found 211.130.

syn: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.83 (m, 1H), 2.56 (m, 1H), 1.72 (m, 1H), 1.48 (m, 1H), 1.43 (s, 9H), 1.17 (d, *J* = 5.95, 3H), 1.12 (d, *J* = 7.33, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.46, 80.54, 65.91, 43.20, 37.32, 28.15, 23.71, 17.84 ppm

IR (neat) 3389, 2976, 1710, 1455, 1359, 1255, 1144, 1029, 850 cm^{-1}

HRMS (ESI) $C_{10}H_{20}O_3$ [2M+Na]$^{+1}$, calculated 399.2701, found 399.1771

4.14 *Tert*-butyl 2-Methyl-4-oxo-4-phenylbutanoate 123

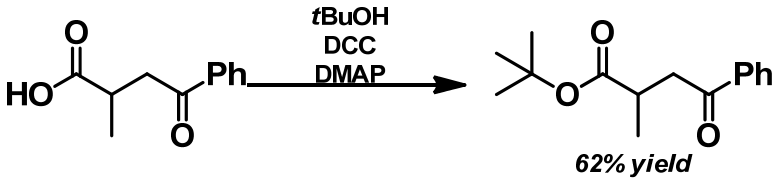


Figure 51. *Tert*-butyl 2-Methyl-4-oxo-4-phenylbutanoate 123

Commercially available 2-methyl-4-oxo-4-phenylbutanoic acid (0.903 g, 4.7 mmol) was esterified with *t*-butanol (1.3 mL, 14 mmol), DCC (1.16 g, 5.6 mmol), and DMAP (0.114 g, 0.93 mmol) in $CHCl_2$ (23 mL). All reagents were placed in a flame-dried flask under argon and stirred for 4 hours at -5 ˚C. The mixture was quenched with hexanes and filtered. The filtrate was concentrated in vacuo and purified via column chromatography (1.5" x 6" silica gel, 10-20% EtOAc in hexanes). 0.441 g of white solid product was obtained (62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (m, 2H), 7.55 (m, 1H), 7.45 (m, 2H), 3.43 (m, 1H), 3.00 (m, 2H), 1.42 (s, 9H), 1.23 (d, *J* = 7.33 Hz, 3H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.38, 175.34, 136.92, 133.16, 128.65, 128.11, 80.39, 42.02, 36.03, 28.08, 17.49 ppm

IR (neat) 2967, 2933, 1728, 1674, 1596, 1447, 1365, 1218, 1150, 1004, 852, 763, 691 cm^{-1}

HRMS (ESI) $C_{15}H_{20}O_3$ [M + Na]$^{+1}$, calculated 271.2921, found 271.1301

4.15 *Tert*-butyl 4-Hydroxy-2-methyl-4-phenylbutanoate 101b

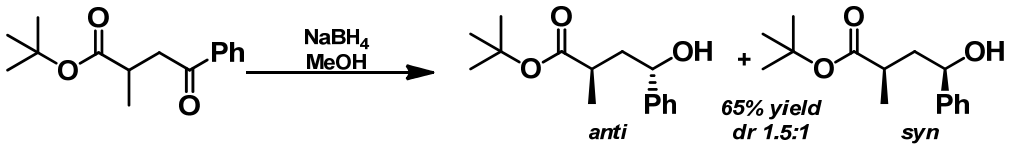


Figure 52. *Tert*-butyl 4-Hydroxy-2-methyl-4-phenylbutanoate 101b

The ketone was then reduced by dissolving sodium borohydride (0.269 g, 7.1 mmol) in dry methanol (6 mL) in a flame-dried round bottom under argon in an ice bath. The ketone (0.447 g, 1.8 mmol) in dry methanol (2 mL) was then added dropwise at 0 ˚C. The reaction was allowed to warm up over one hour then was quenched with 1M HCl (ph ~2). The methanol was removed in vacuo and the aqueous layer was extracted with $CHCl_2$ (3 x 5 mL). The combined organic layers were dried and concentrated in vacuo. Purification was done via column chromatography (1" x 7" silica gel, 20% EtOAC in hexanes) to yield 0.289 g colorless oil mixture of diastereomers (65%, dr 1.5:1).

anti: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.68 (m, 1H), 2.59 (m, 1H), 2.44 (m, 1H), 2.16 (m, 1H), 1.44 (s, 9H), 1.15 (d, *J* = 3.44, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.54, 144.71, 128.55, 127.67, 125.96, 80.40, 72.88, 43.02, 38.06, 28.13, 17.70

IR (neat) 3427, 2975, 2934, 1724, 1455, 1366, 1149, 1028, 846, 699 cm^{-1}

syn: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (m, 5H), 4.75 (m, 1H), 2.02 (m, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.46 (s, 9H), 1.14 (d, *J* = 3.44, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 28.17, 32.10, 34.03, 55.38, 73.41, 80.60, 113.91, 127.09, 136.44, 159.11, 173.45 ppm

IR (neat) 3429, 2975, 2934, 1723, 1454, 1366, 1149, 1028, 698 cm^{-1}

4.16 Lactone 127

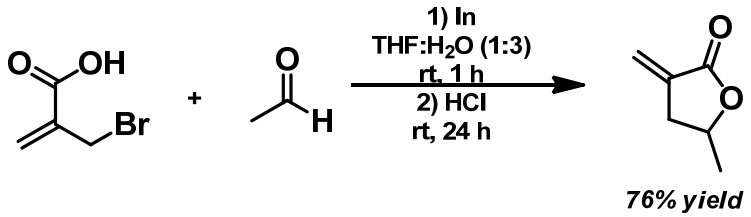


Figure 53. Lactone 127

2-(Bromomethyl)acrylic acid (0.5 g, 3 mmol) was dissolved in THF:H_2O (1:3, 0.75 mL: 2.25 mL). Indium metal (0.34 g, 3 mmol) and acetaldehyde (0.17 mL, 3 mmol) were added and the reaction mixture was stirred at rt for 1 h. 6M HCl (2.3 mL, 68 mmol) was added to the reaction and the mixture was stirred at rt overnight. The reaction was extracted with EtOAc (3 x 10 mL). The organic layer was dried over Mg_2SO_4, filtered, and concentrated in vacuo yielding yellow oil (0.254 g, 76%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (t, *J* = 2.86, 1H), 5.61 (t, *J* = 2.58, 1H), 4.65 (dt, *J* = 7.45, 6.30, 1H), 3.07 (m, 1H), 2.52 (m, 1H), 1.40 (d, *J* = 6.30 Hz, 3H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.47, 134.93, 122.22, 74.07, 35.24, 22.09 ppm

IR (neat) 1755, 1665, 1386, 1256, 1084, 1036, 951, 813 cm^{-1}

HRMS ($C_8H_{14}O_3$, ESI) $[M+H]^+$, calculated 113.1373, found 113.0601

4.17 Lactone 128

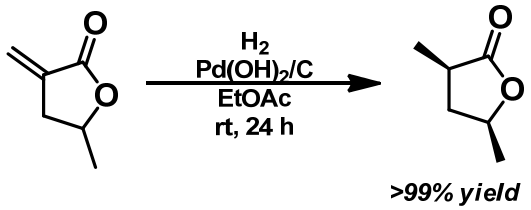


Figure 54. Lactone 128

To lactone **127** (0.254 g, 2.27 mmol) in EtOAc (23 mL) was added $Pd(OH)_2/C$ (0.025 g, 10% by weight of intermediate) was added. The reaction flask was flushed of all gases and then a balloon of H_2 was added to the flask. The reaction was stirred overnight at room temperature. The mixture was filtered through a pad of Celite ® and concentrated in vacuo to afford compound **128** as a colorless oil (0.258 g, >99%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (dt, *J* = 10.76, 5.61 Hz, 1H), 2.66 (m, 1H), 2.49 (m, 1H), 1.47 (m, 1H), 1.39 (d, *J* = 6.41, 3H), 1.25 (d, *J* = 6.87, 3H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.80, 75.06, 39.17, 36.49, 21.00, 15.19 ppm

IR (neat) 1768, 1736, 1373, 1239, 1177, 1042, 950 cm^{-1}

HRMS (ESI) $C_8H_{14}O_3$ $[M+H]^+$ calculated 115.1428, found 115.0756

4.18 Ether 129

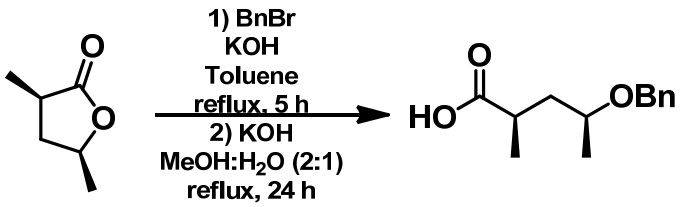


Figure 55. Ether 129

Crushed KOH (0.685 g, 12.2 mmol) was added to a toluene (10 mL) solution of lactone **128** (0.258 g, 2.3 mmol) and benzyl bromide (1.1 mL, 9.2 mmol). The reaction mixture was stirred at 110 ˚C for 5 h and then toluene was removed in vacuo. Next, methanol (10 mL) was added to reaction flask followed by crushed KOH (0.219 g, 3.9 mmol) and water (5 mL) then the reaction mixture was refluxed for 16 h. The reaction mixture was extracted with diethyl ether (3 x 10 mL), the aqueous layer was acidified with concentrated HCl, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over Mg_2SO_4, filtered, and concentrated in vacuo to give the product as a pale yellow oil (0.276 g, 54%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.40 (s, 2H), 3.58 (m, 1H), 2.63 (m, 1H), 1.44 (m, 2H), 1.22 (d, *J* = 5.95, 3H), 1.13 (d, *J* = 7.33, 3H) ppm

^{13}C NMR (126 MHz, $CDCl_3$) δ 182.96, 138.54, 128.44, 127.86, 127.63, 72.69, 70.39, 40.55, 36.61, 19.65, 17.21 ppm

IR (neat) 3030, 2972, 2935, 1703, 1454, 1287, 1091, 950, 735, 697 cm^{-1}

HRMS (ESI) $C_8H_{14}O_3$ $[M-H]^-$ calculated 221.2727, found 221.1178

4.19 Protected Ester 130

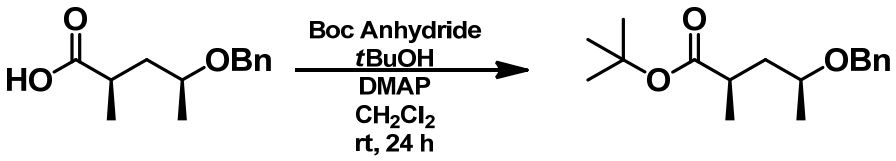


Figure 56. Protected Ester 130

To a solution of ether intermediate **1129** (0.276 g, 1.2 mmol), DMAP (0.146 g, 1.2 mmol), and *t*-butanol (0.33 mL, 3.6 mmol) in CH_2Cl_2 was added boc anhydride (0.262 g, 1.2 mmol). The reaction mixture was stirred at rt overnight. The solvent was then removed in vacuo. Column chromatography (1" x 5" silica gel, 0-10% EtOAc in Hexanes) afforded product (0.150 g, 45%).

4.20 Synthesis of 101a$_{syn}$

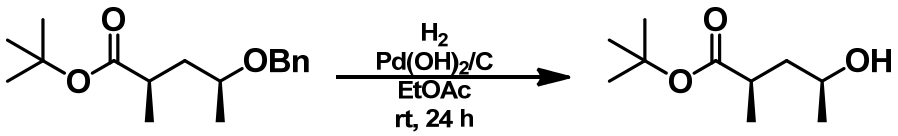


Figure 57. Synthesis of 101a$_{syn}$

To intermediate **130** (0.150 g, 0.5 mmol) in EtOAc (5 mL) was added $Pd(OH)_2/C$ (0.015 g, 10% by weight of intermediate) was added. The reaction flask was flushed of all gases and then a balloon of H_2 was added to the flask. The reaction was stirred overnight at room temperature. The mixture was filtered through a pad of Celite ® and concentrated in vacuo to afford compound as a

colorless oil (0.083 g, 89%). The analytical data for this compound can be found under compound **101a**.

4.21 Large Scale Lactonization of 101a$_{syn}$

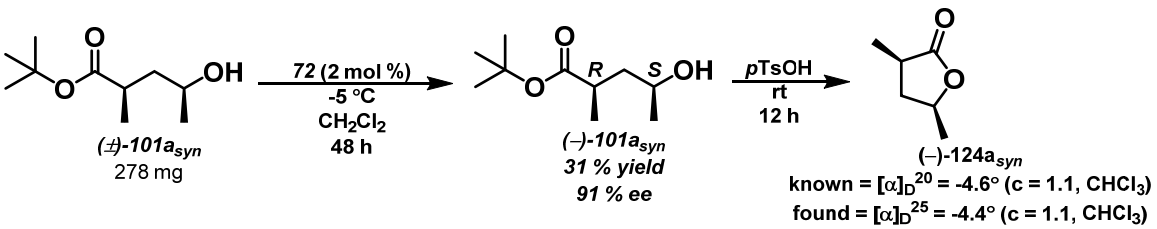


Figure 58. Large Scale Lactonization of 101a$_{syn}$

Hydroxy ester 101asyn (278 mg, 1.25 mmol) was dissolved in CH2Cl2 (50 mL) and catalyst 72 (18.8 mg, 0.025 mmol) was added to the reaction mixture. The mixture was stirred for 48 hours and quenched with EtOAc. Solvent was removed in vacuo and the crude mixture was purified via column chromatography (0.5” x 4” silica gel, 0-10% EtOAc/Hexanes) yielding a light yellow oil (31%, 99% ee). Enantioenriched hydroxy ester (10 mg, 0.05 mmol) was dissolved in CH2Cl2 (5 mL) and p-toluenesulfonic acid (0.02 mg, 0.001 mmol) was added. The yielded lactone was then used to determine absolute configuration.

4.22 General Procedure for Lactonization on GC Scale

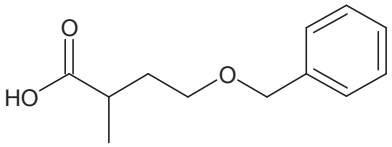
To an oven dried screw-caped vial was introduced anhydrous solvent (10 mL), and hydroxyester (10 mg, 0.057 mmol). To the vial was added 1 mL of internal standard (226 mg xylene in 500 mL CH2Cl2). The vial was conditioned to

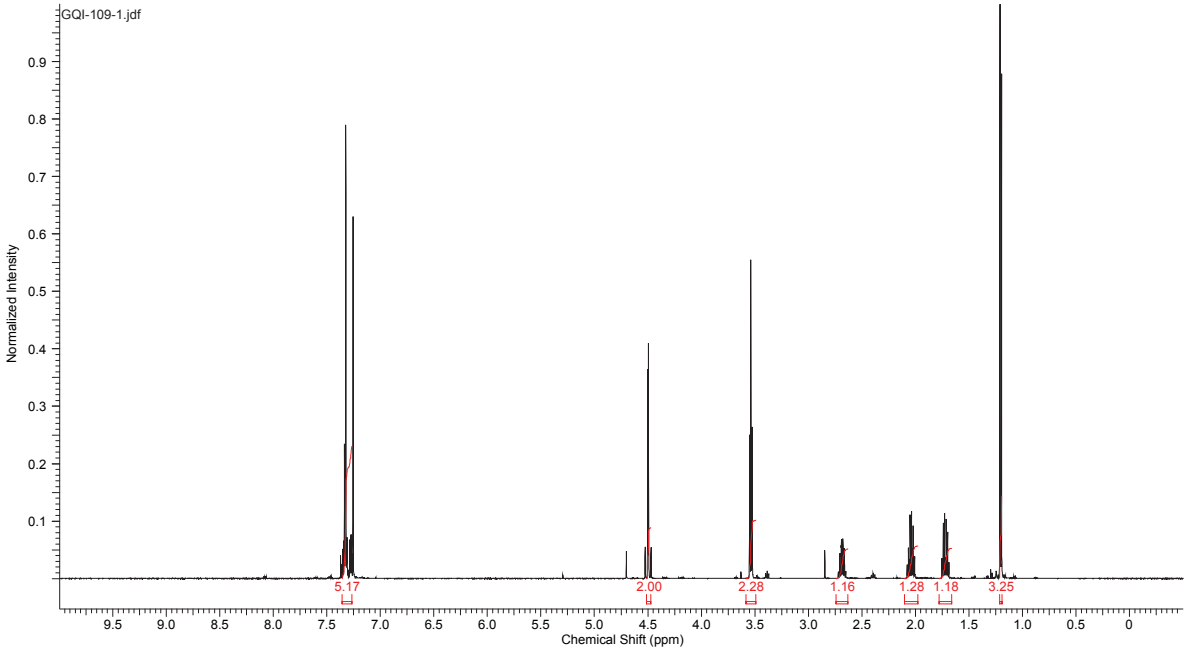
the experiment temperature for 10 min and an initial time point was taken, after which catalyst (1.0 mg, 0.0013 mmol) was added and the reaction mixture was aged at experiment temperature. Aliquots were taken for chiral GC analysis.

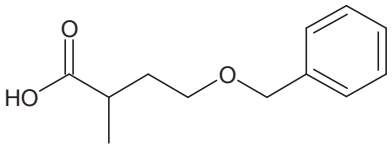
APPENDIX A

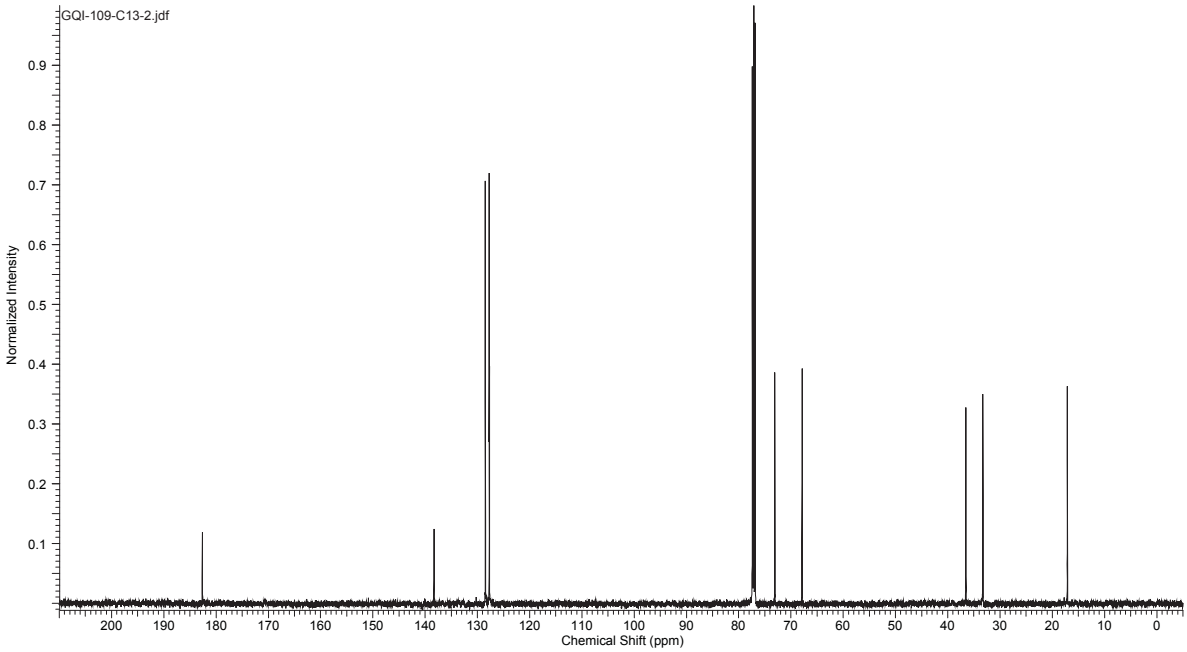
NMR SPECTRA OF COMPOUNDS

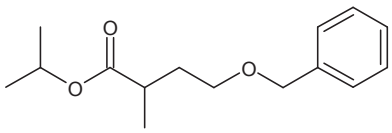
NMR spectra were recorded using a JEOL ECA spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). All spectra were taken at room temperature in deuterated chloroform unless otherwise noted.

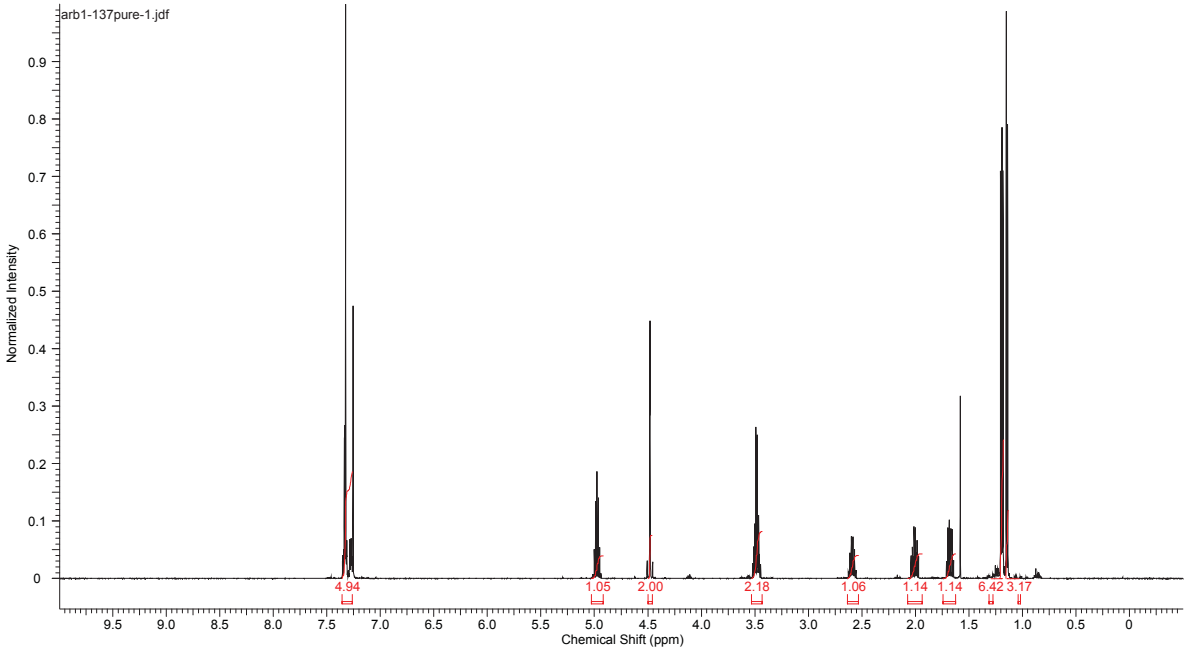


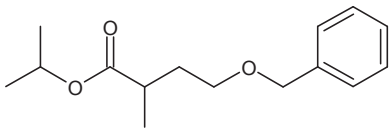


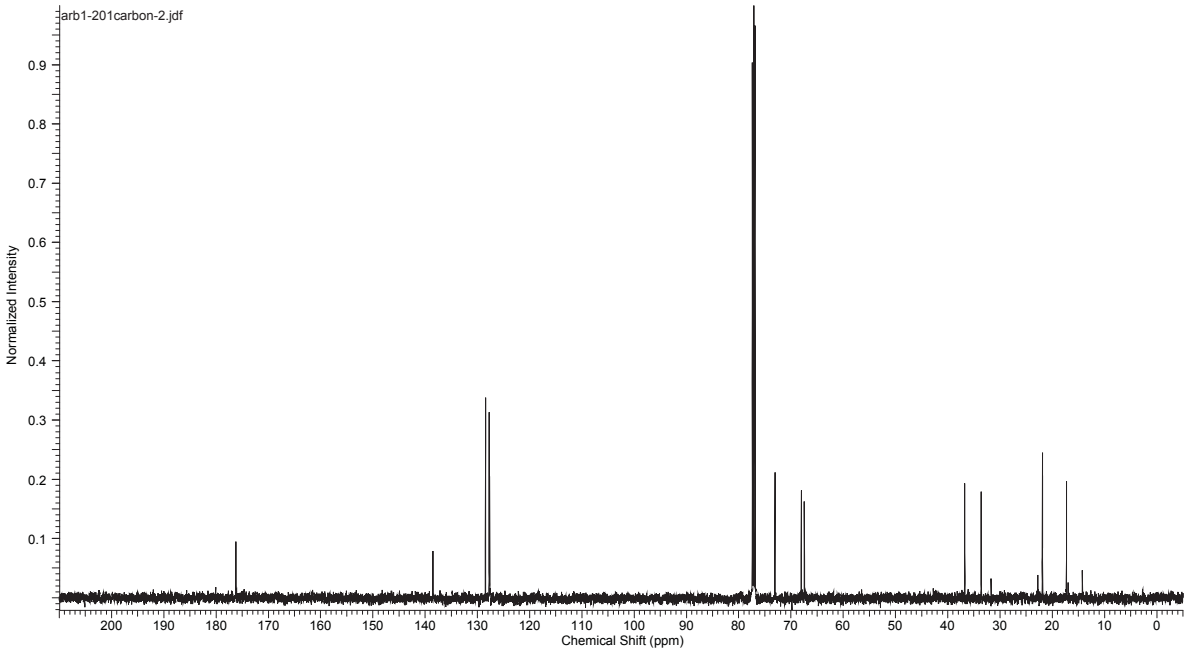


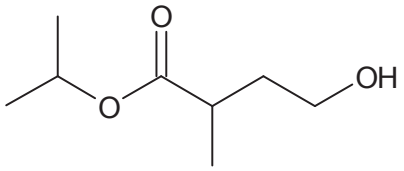


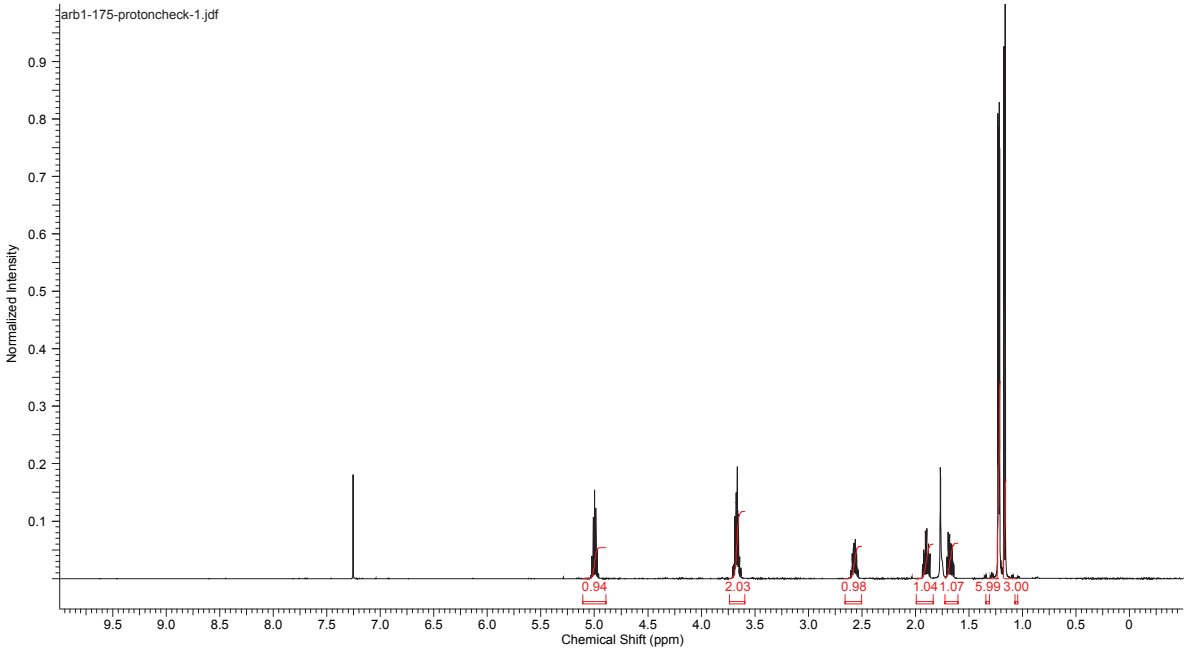


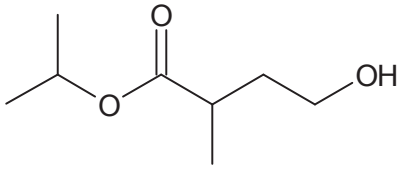


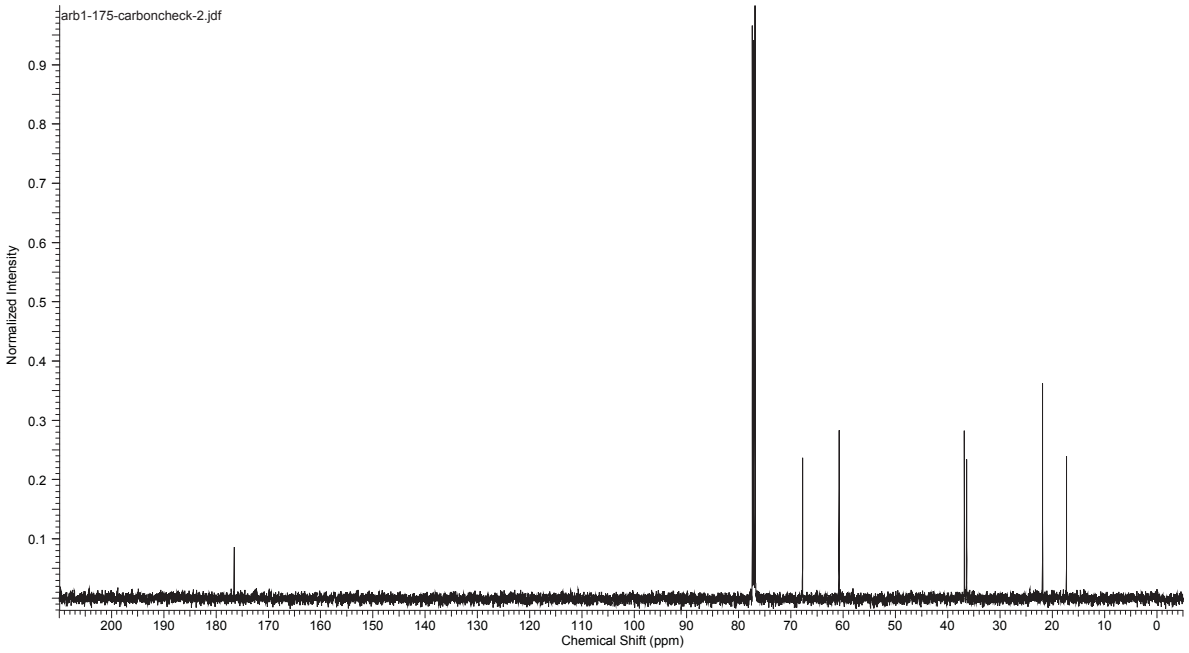


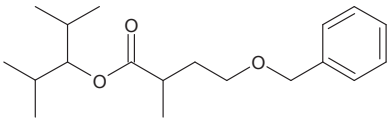


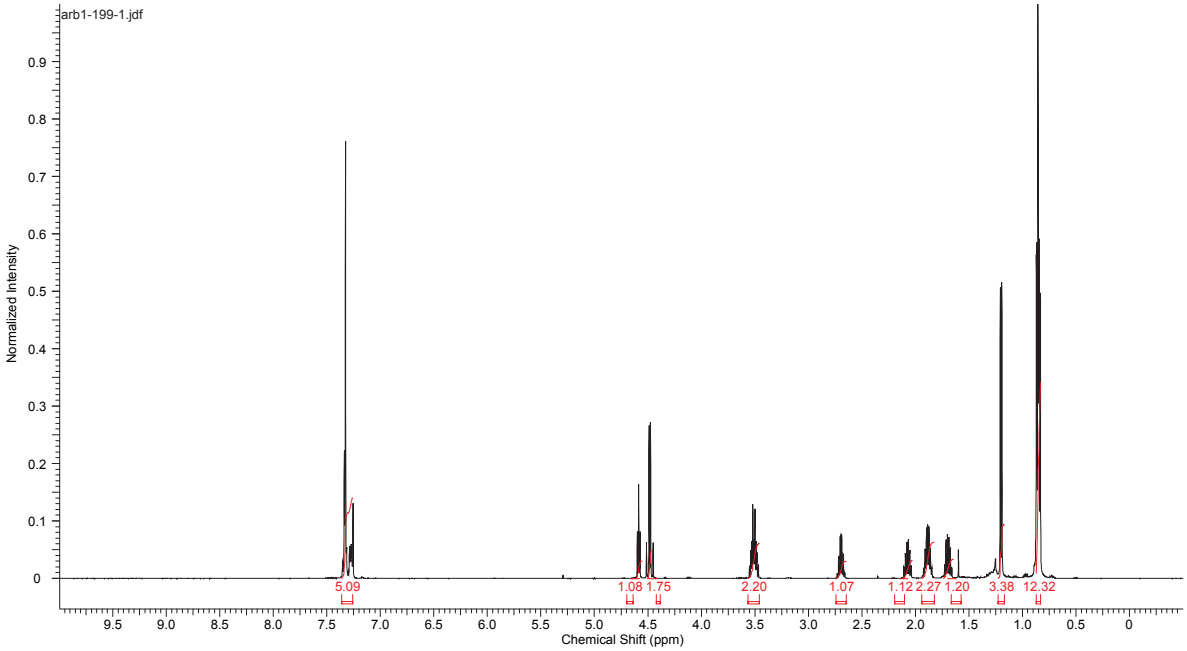


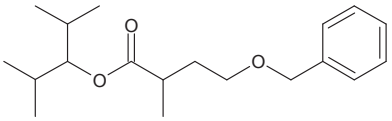


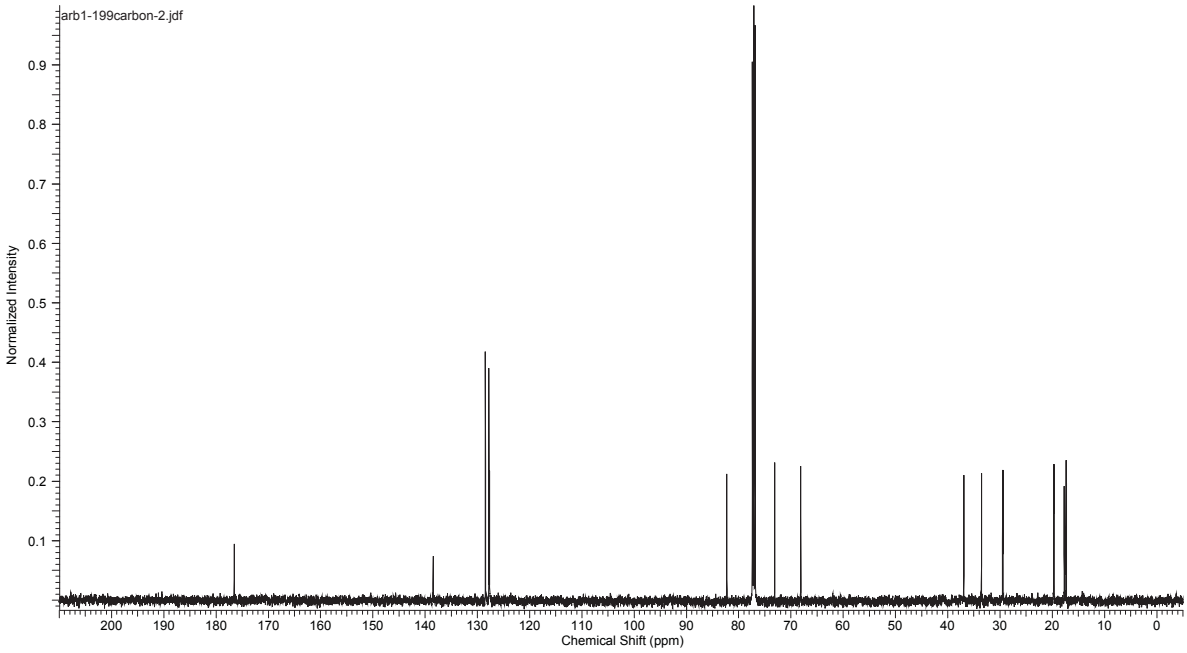


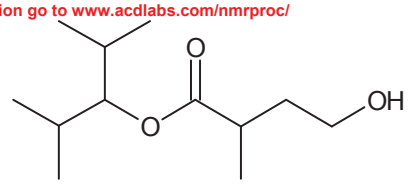


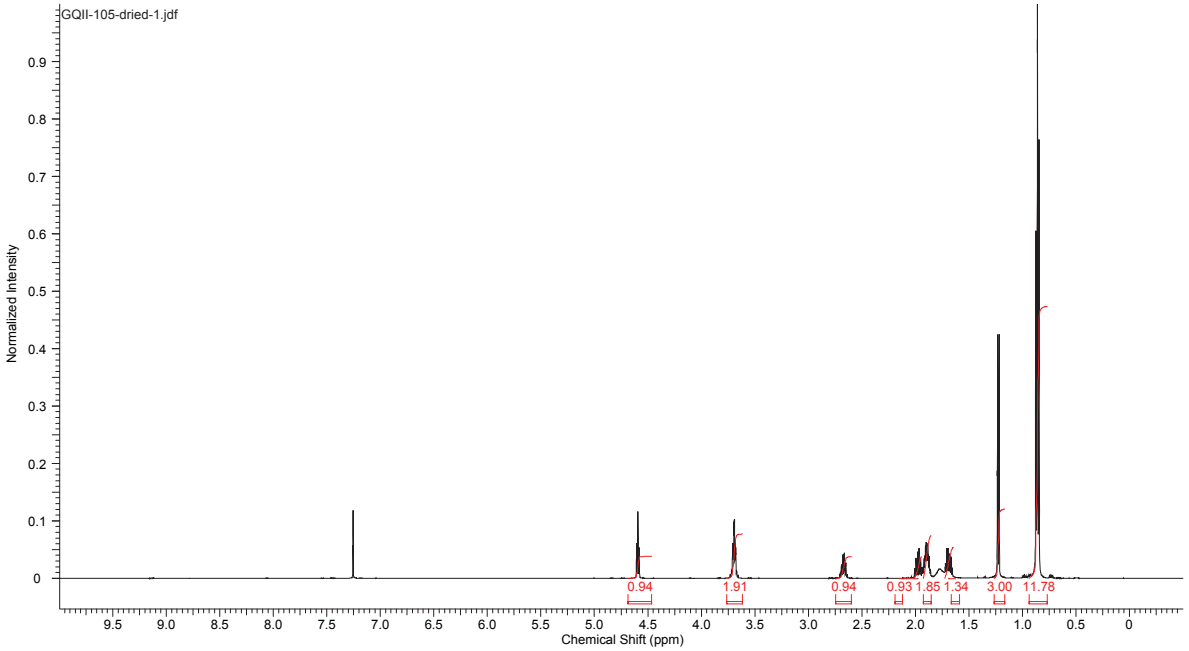


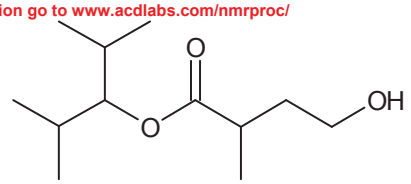


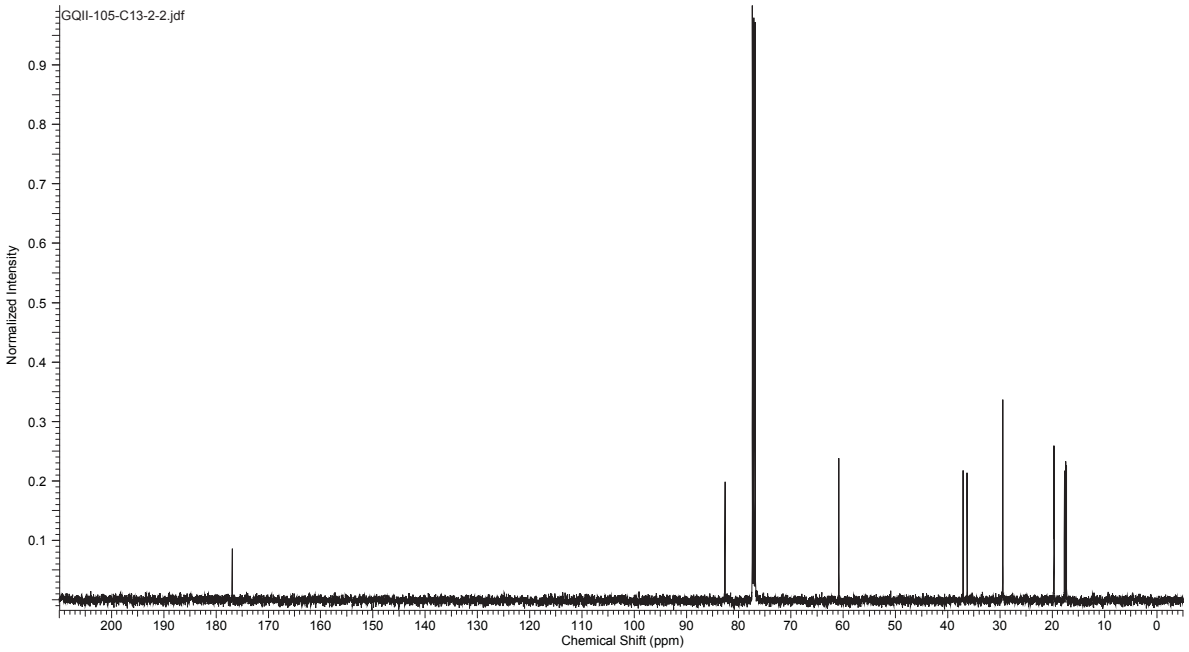


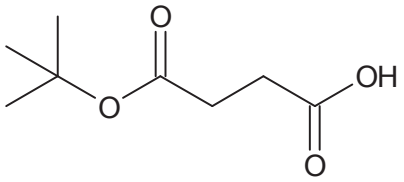


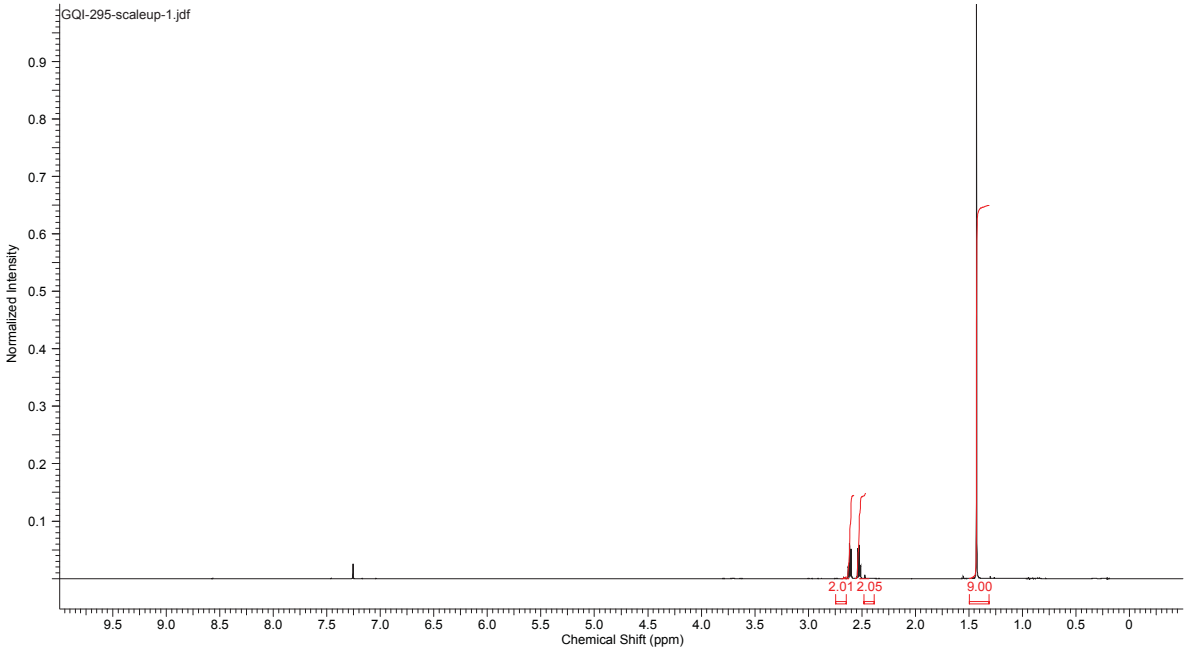


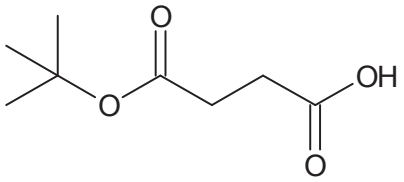


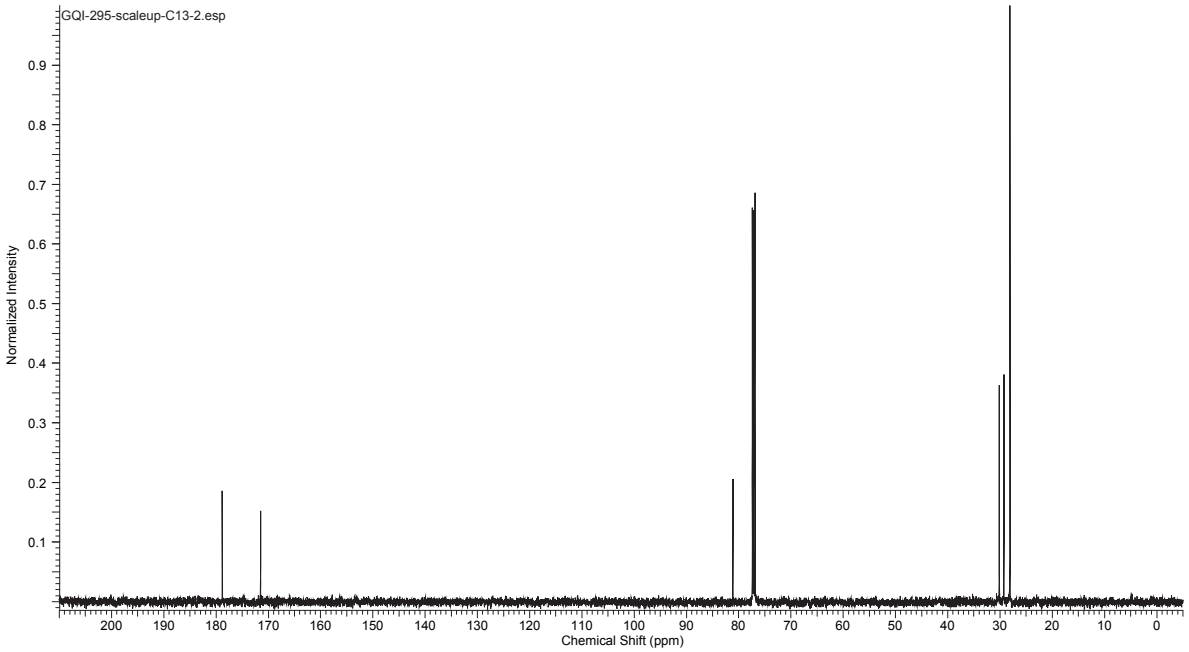


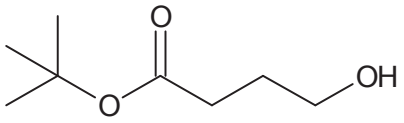


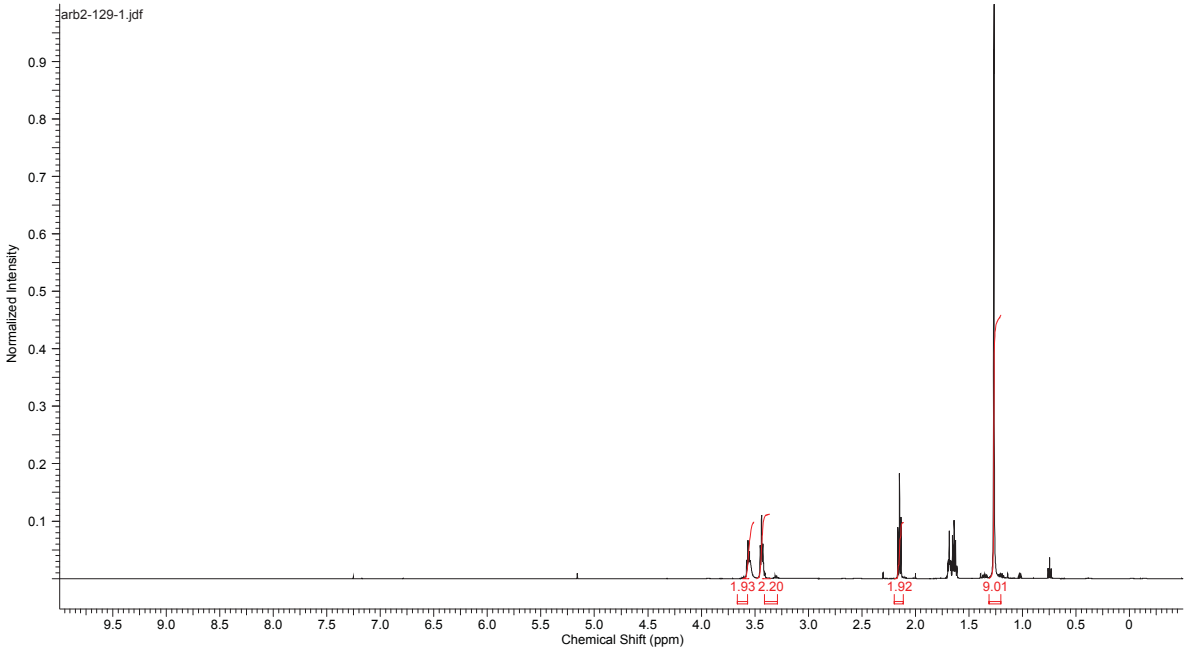




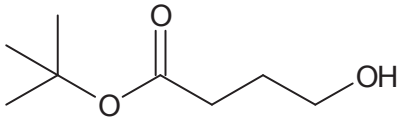


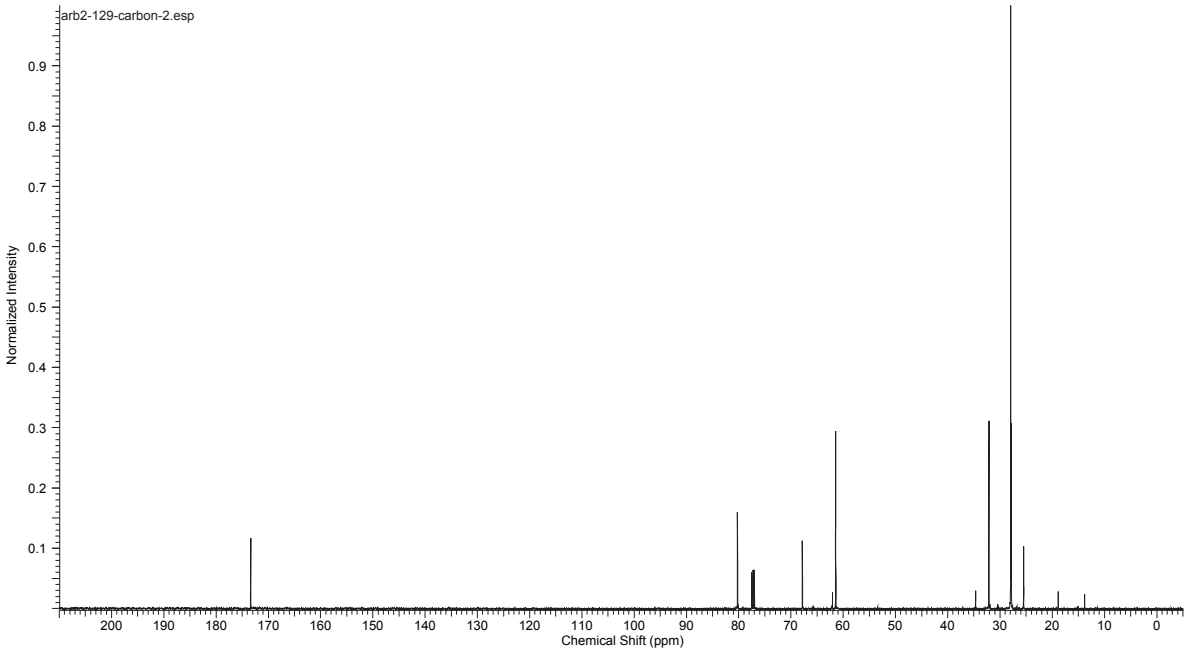


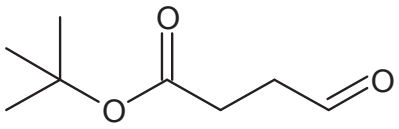


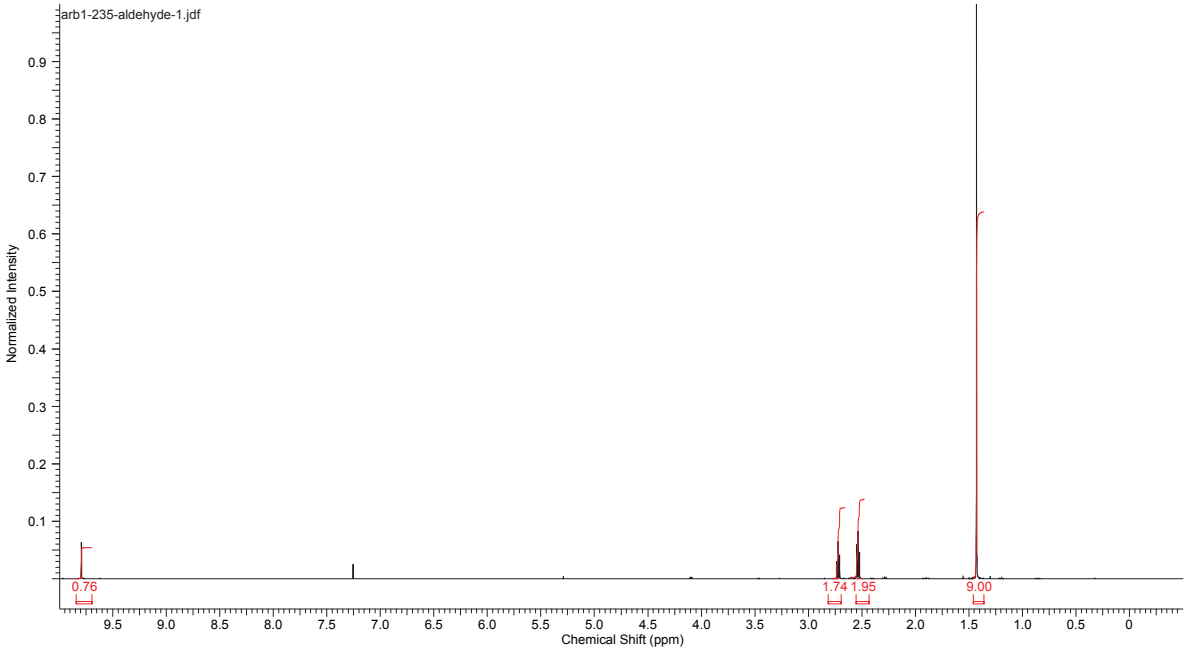


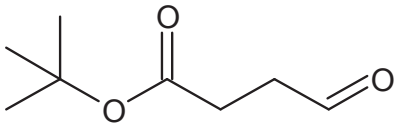
This report was created by ACD/NMR Processor Academic Edition. For more information go to www.acdlabs.com/nmrproc/

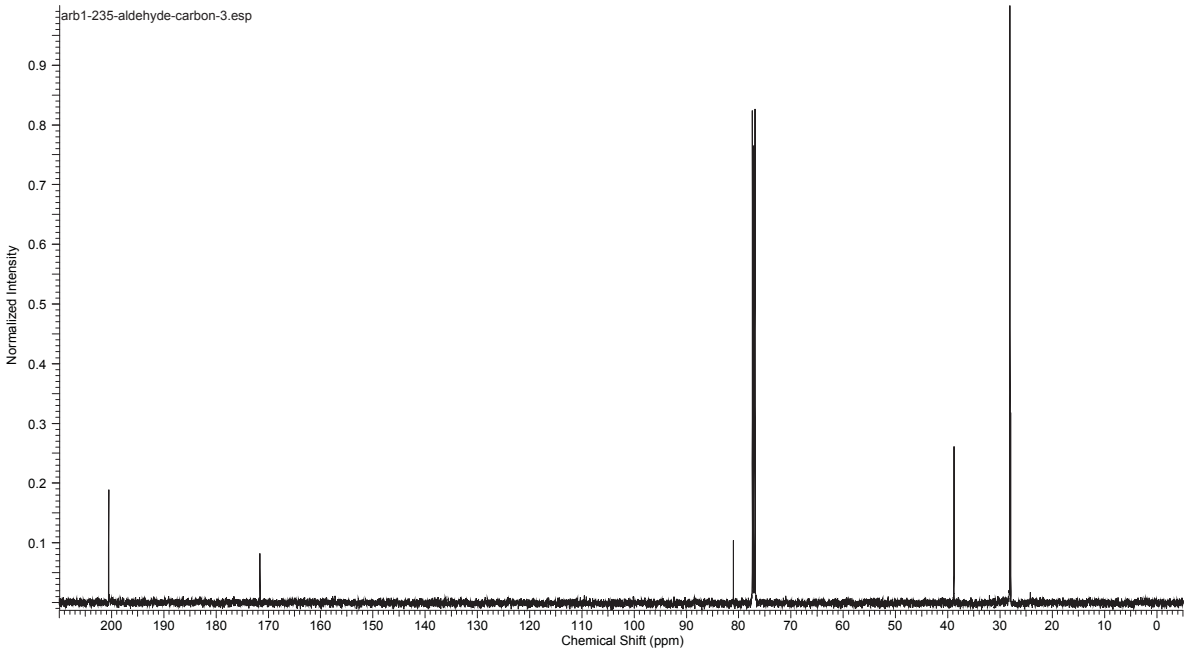


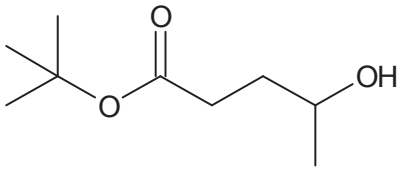


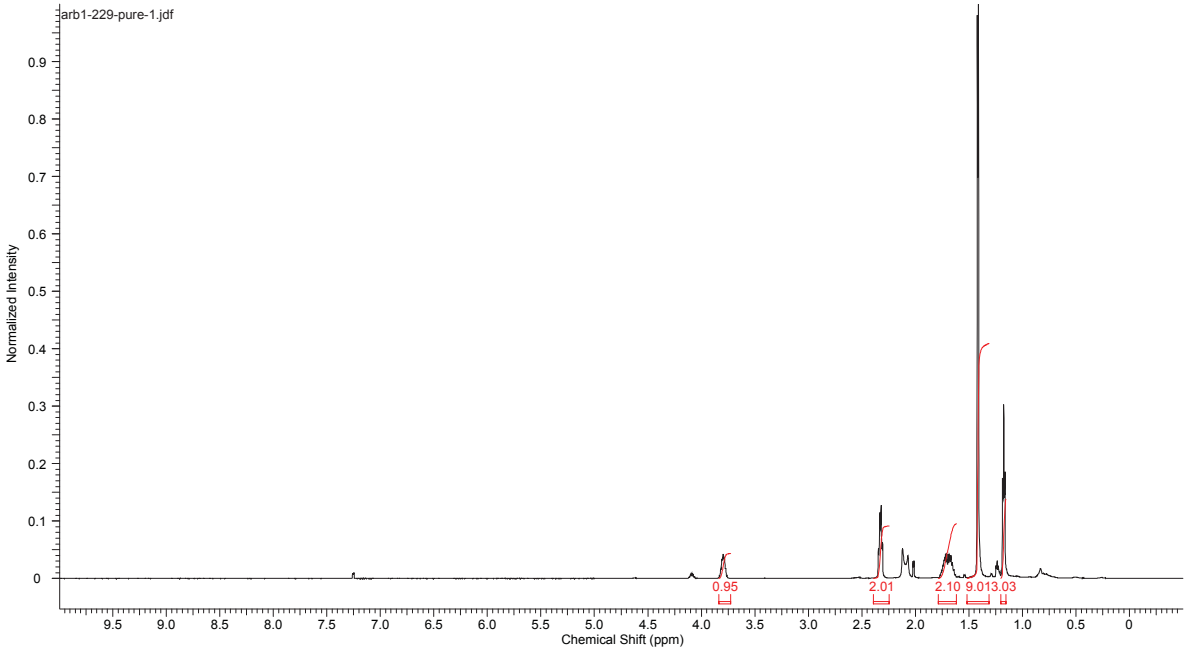


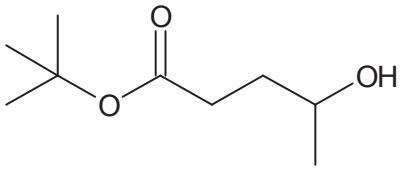


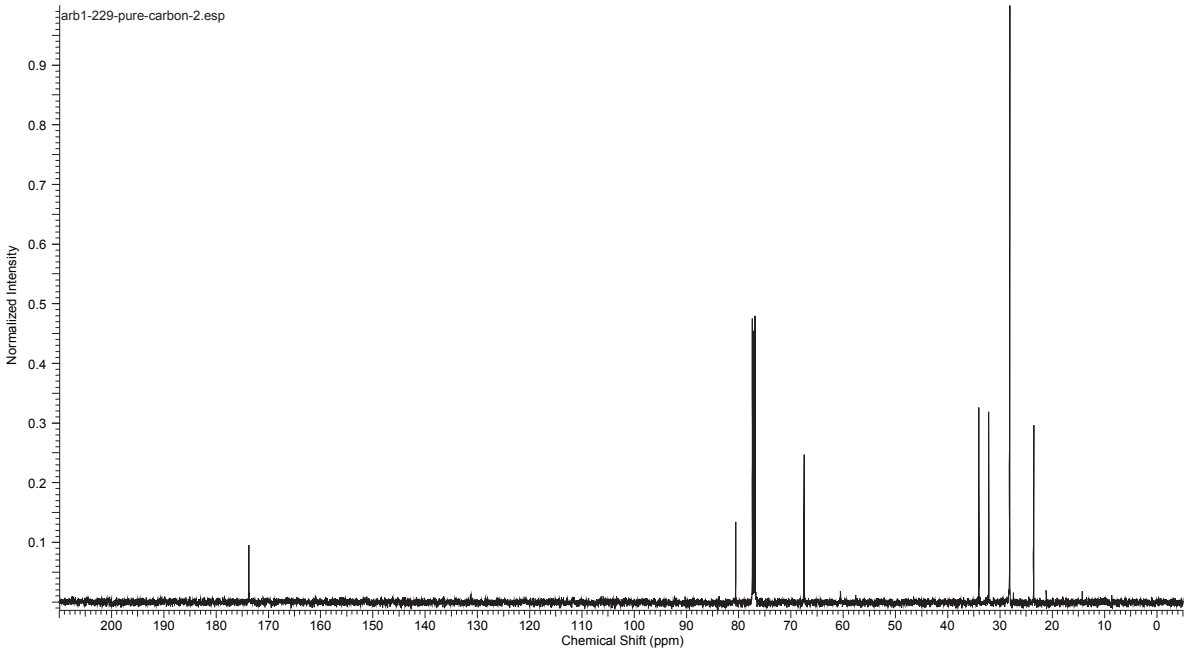


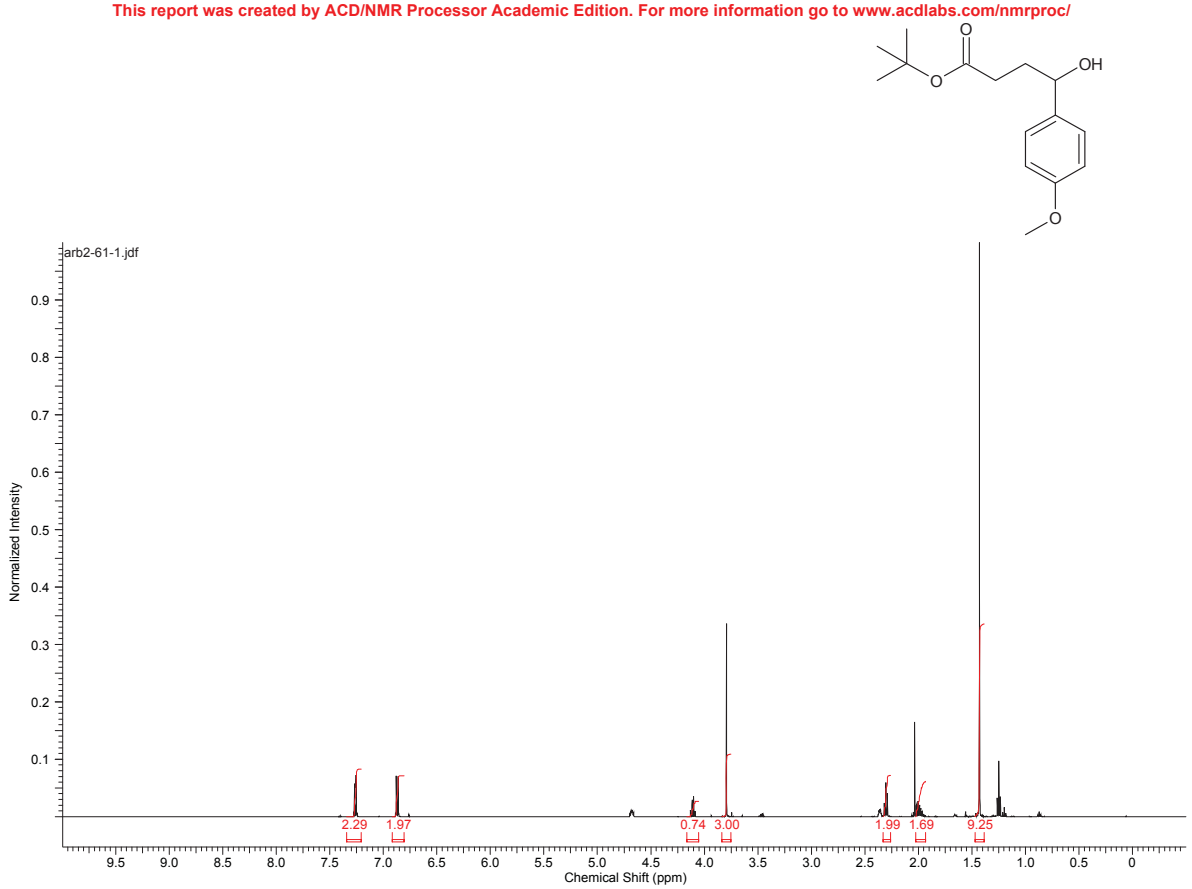


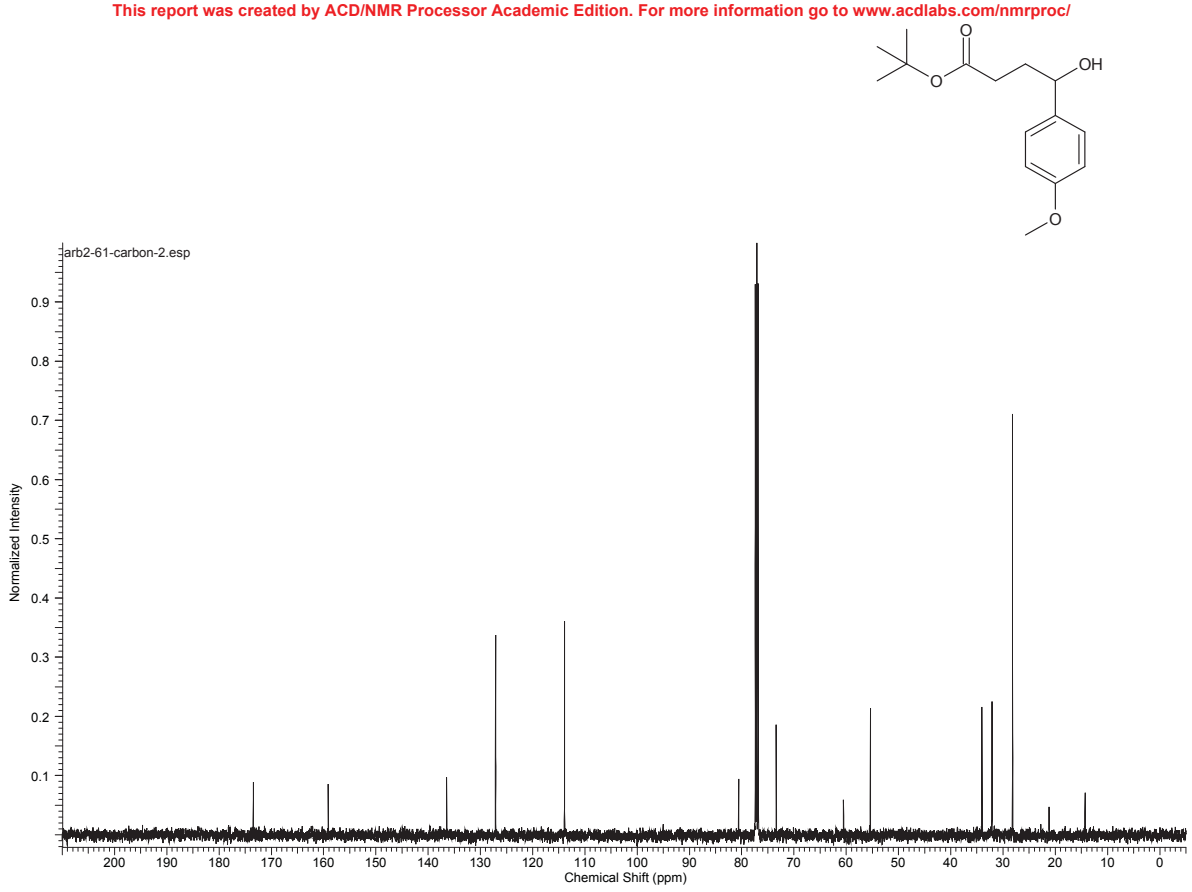


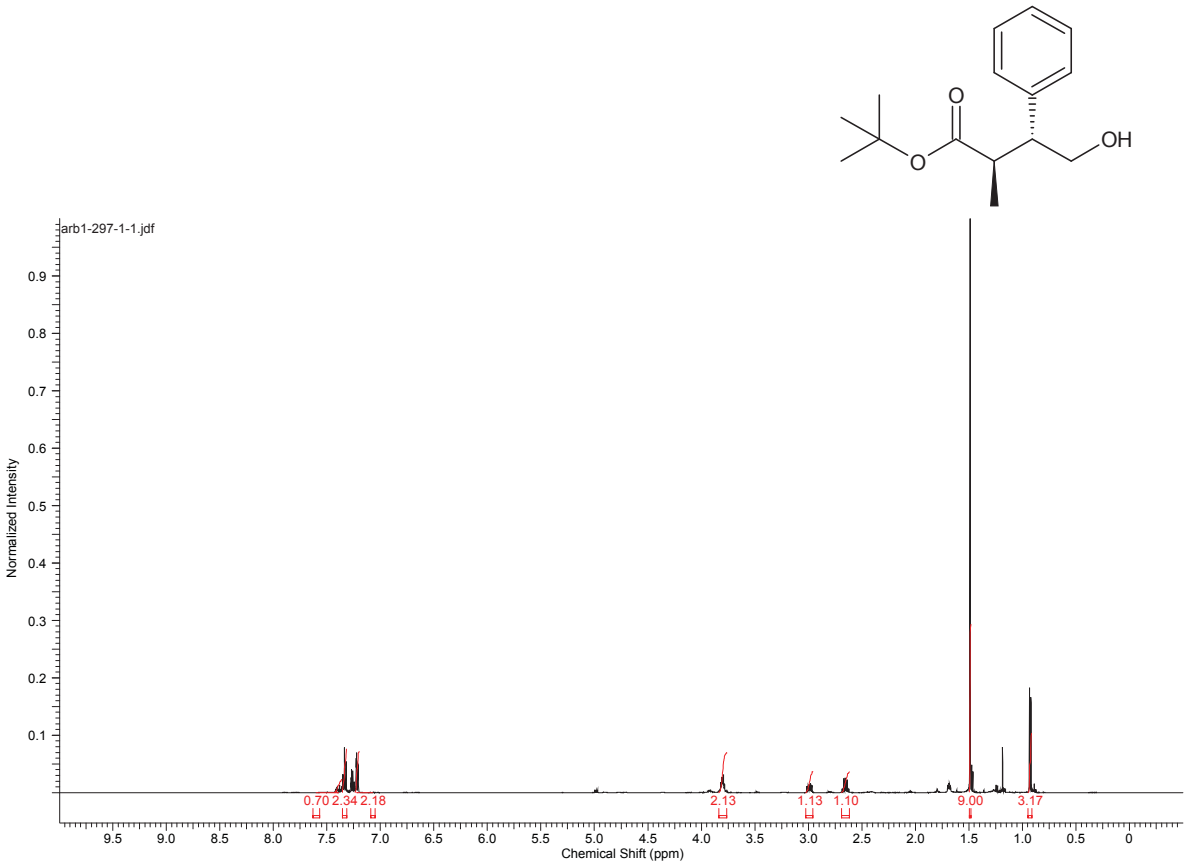


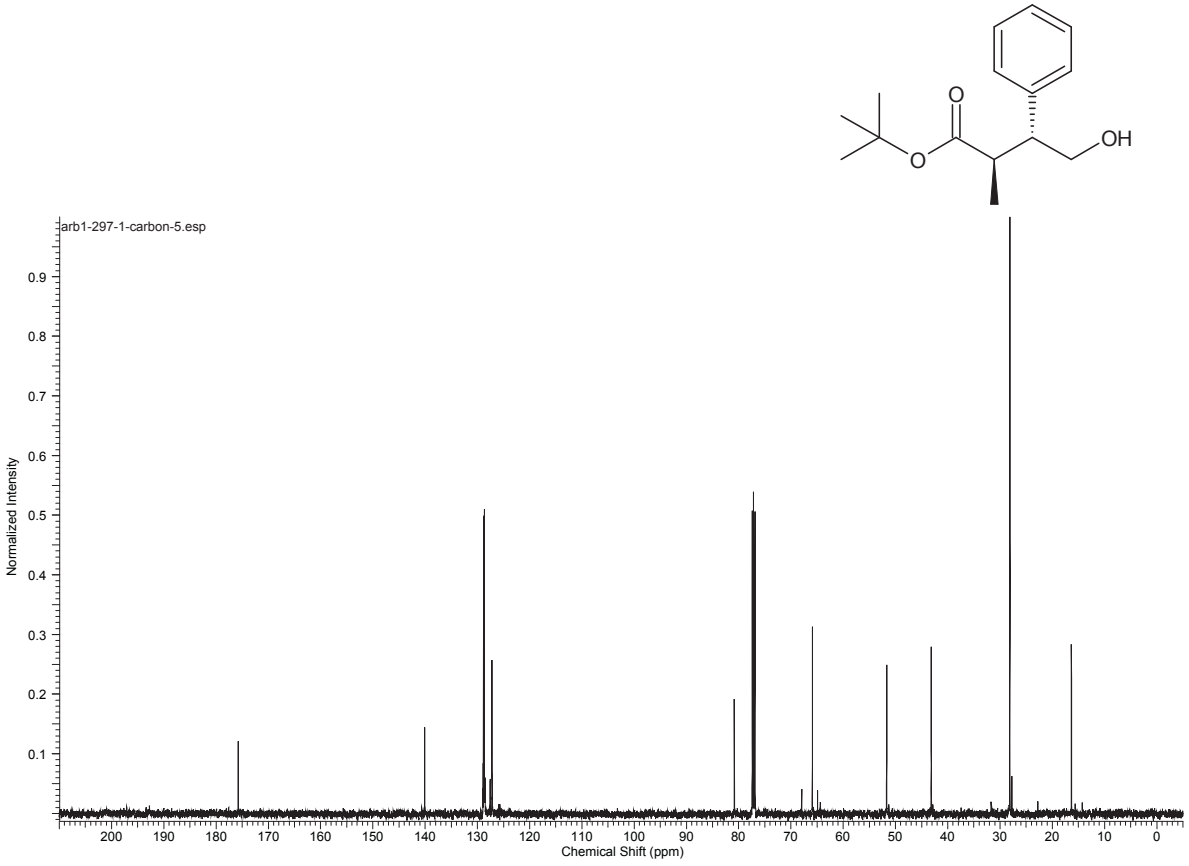


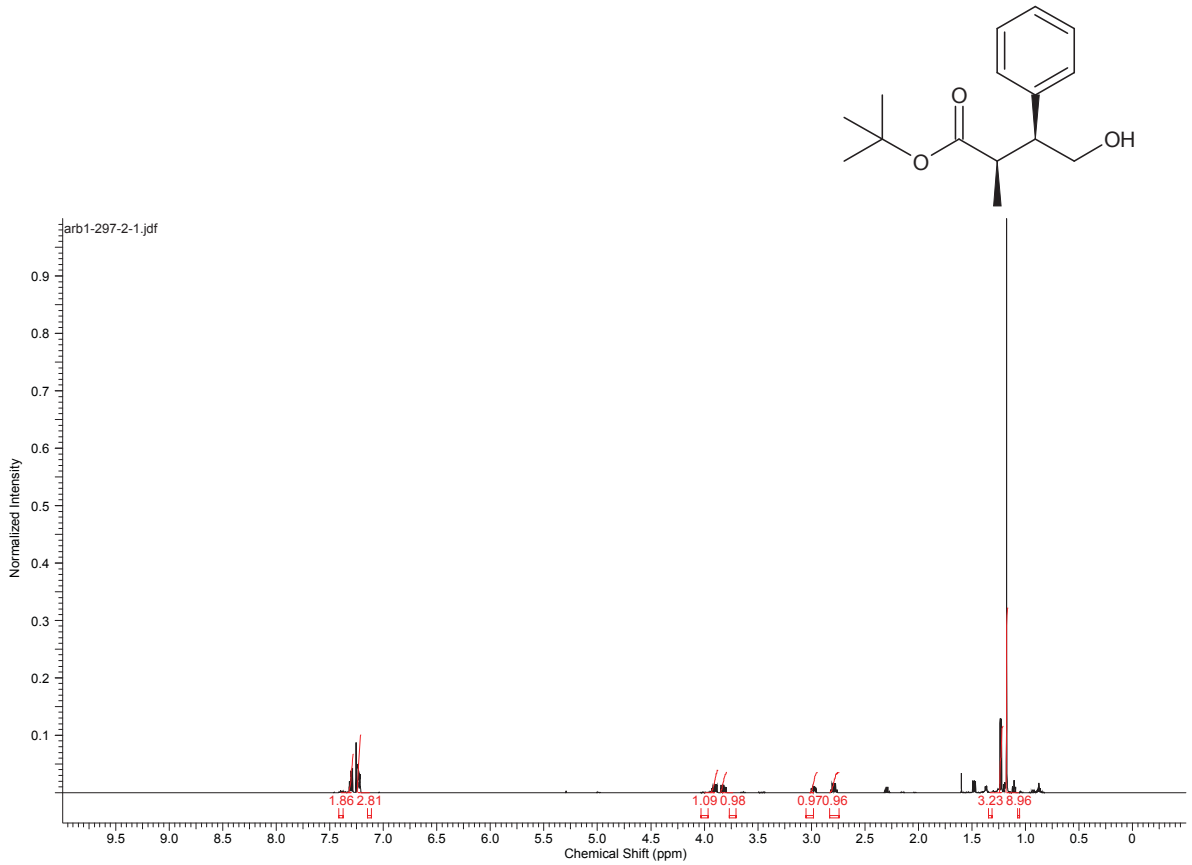




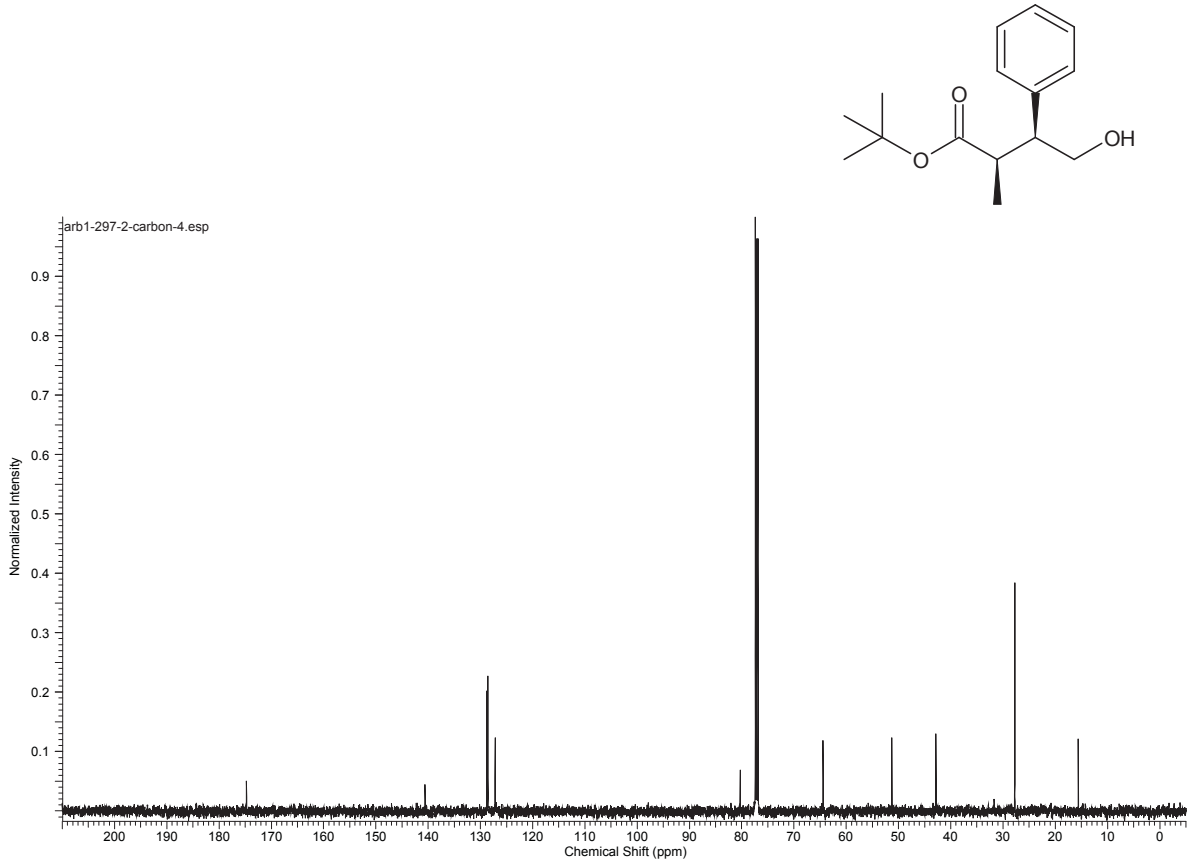


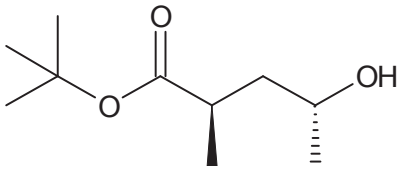


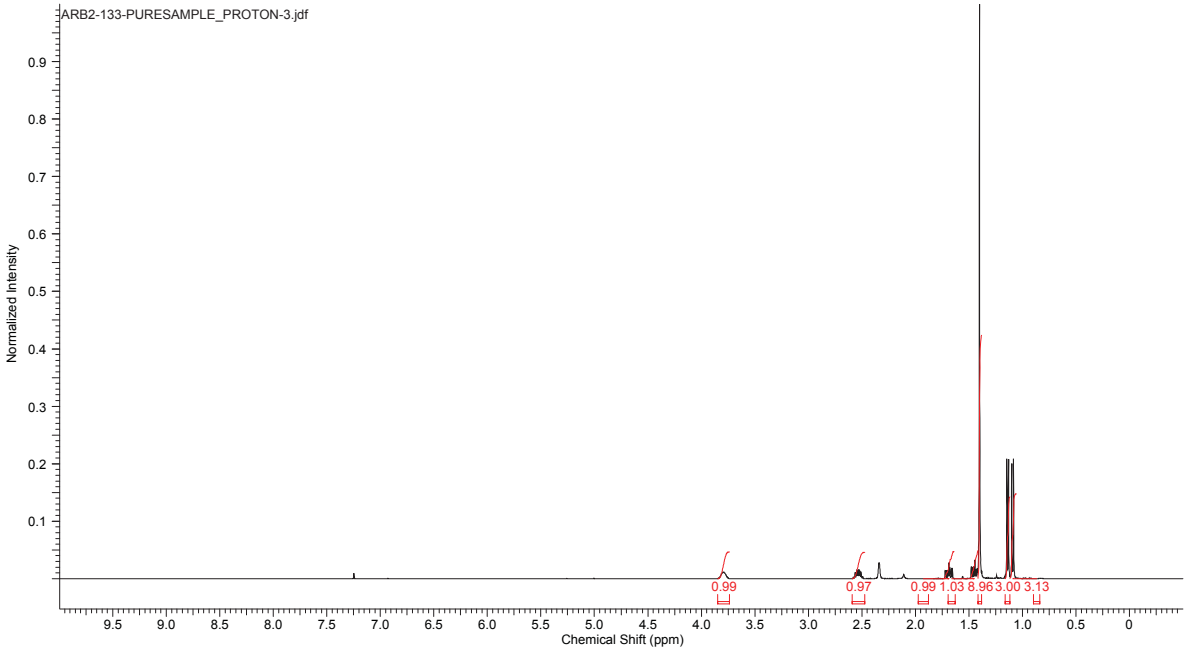


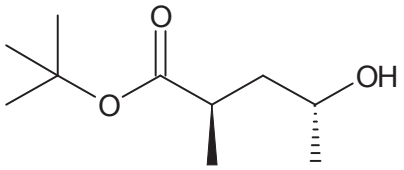


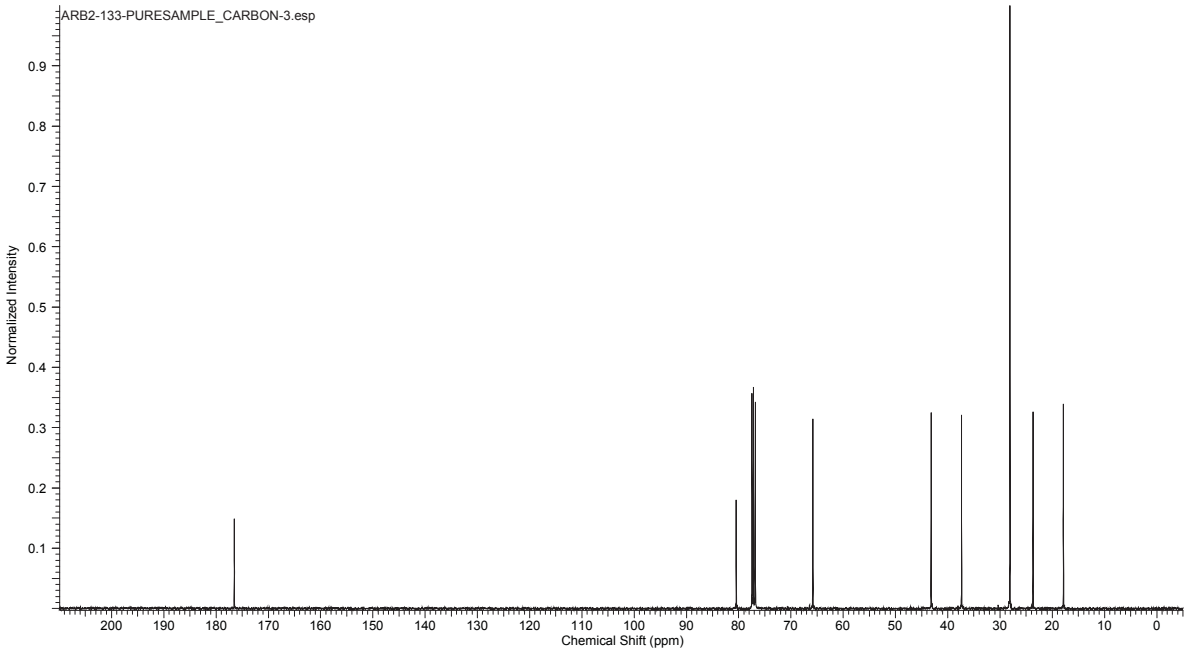
This report was created by ACD/NMR Processor Academic Edition. For more information go to www.acdlabs.com/nmrproc/

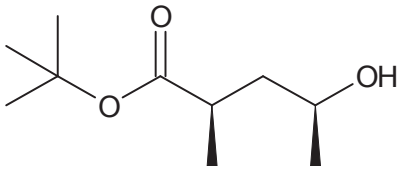


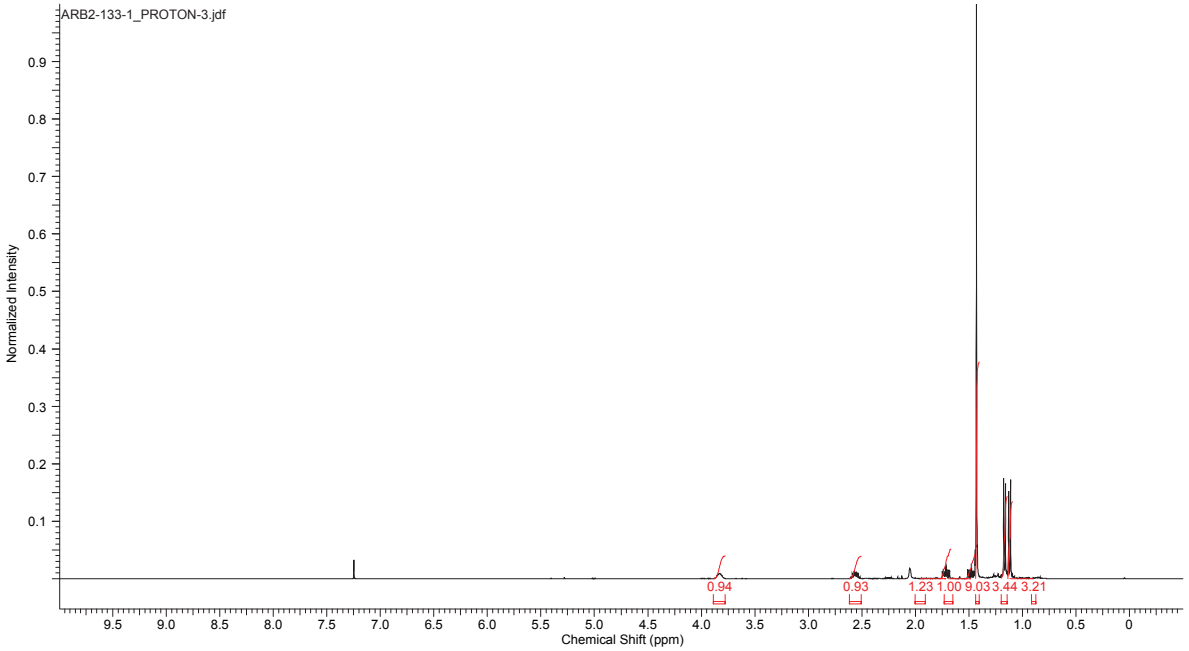


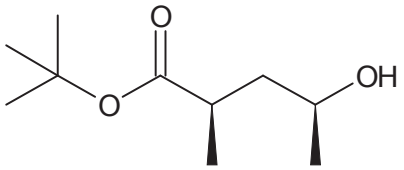


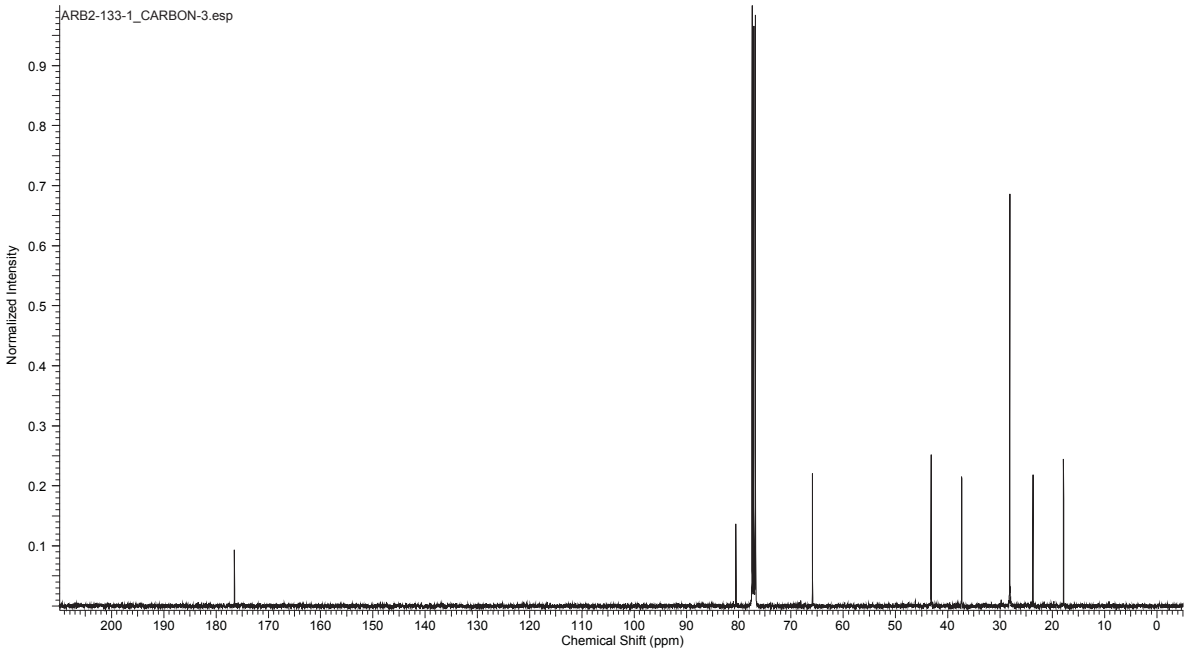


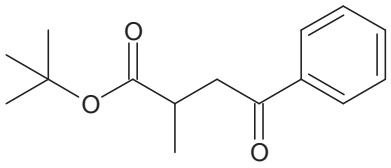


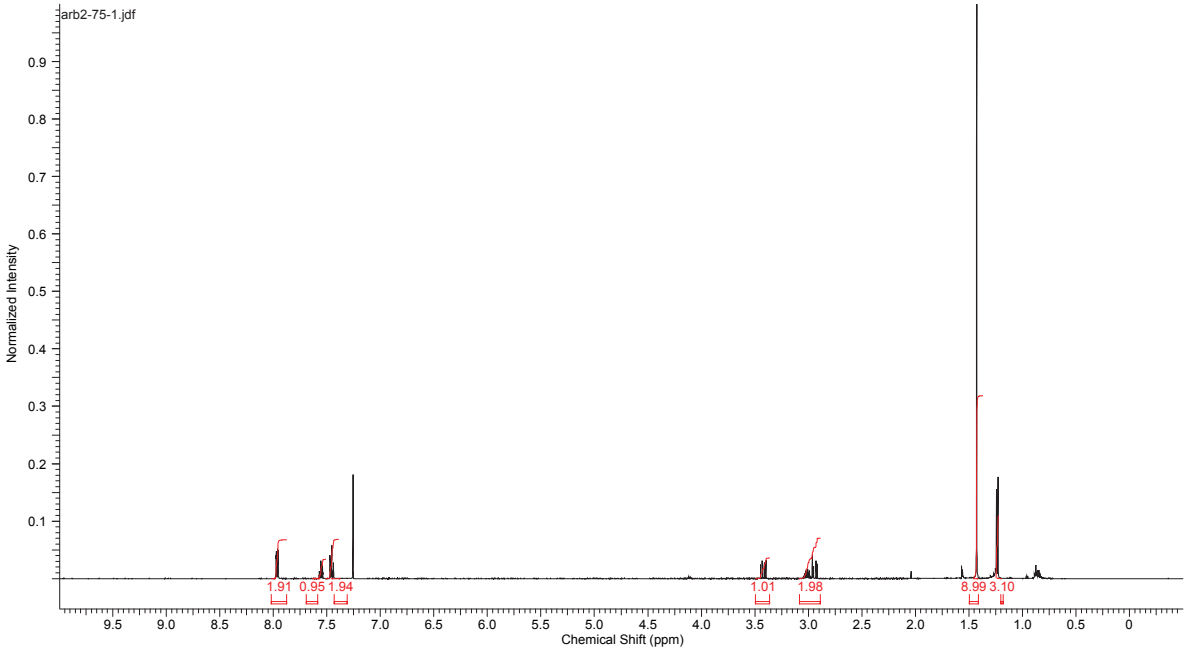


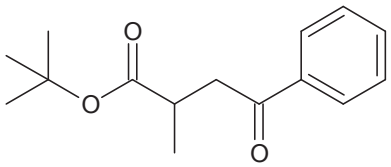


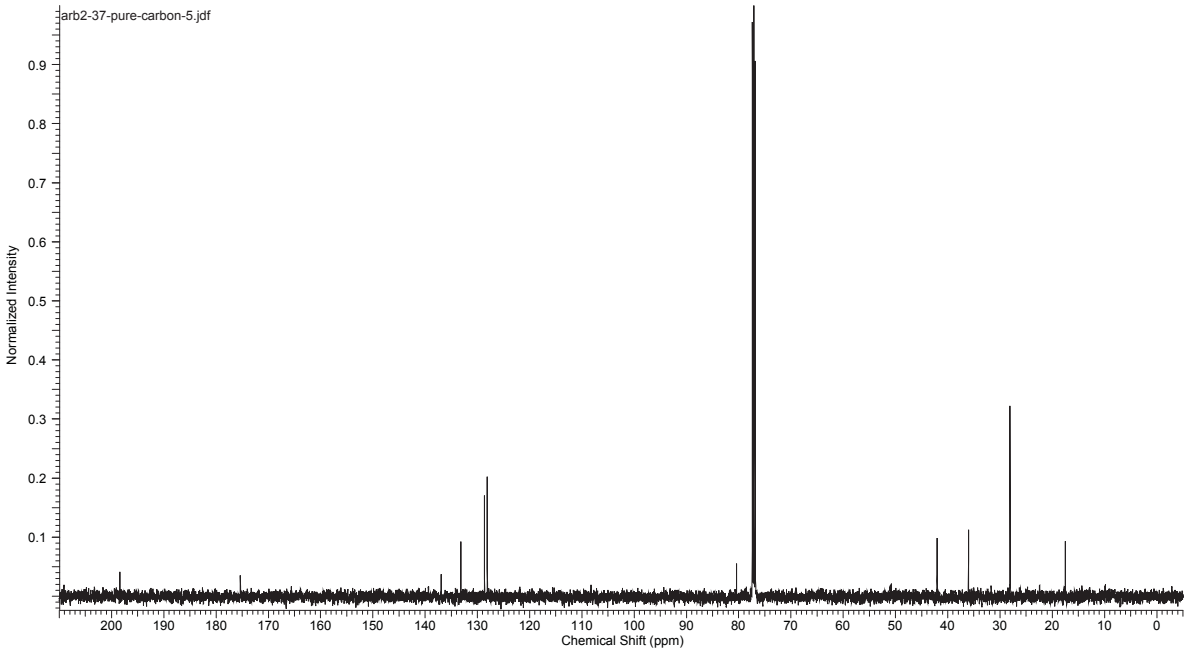


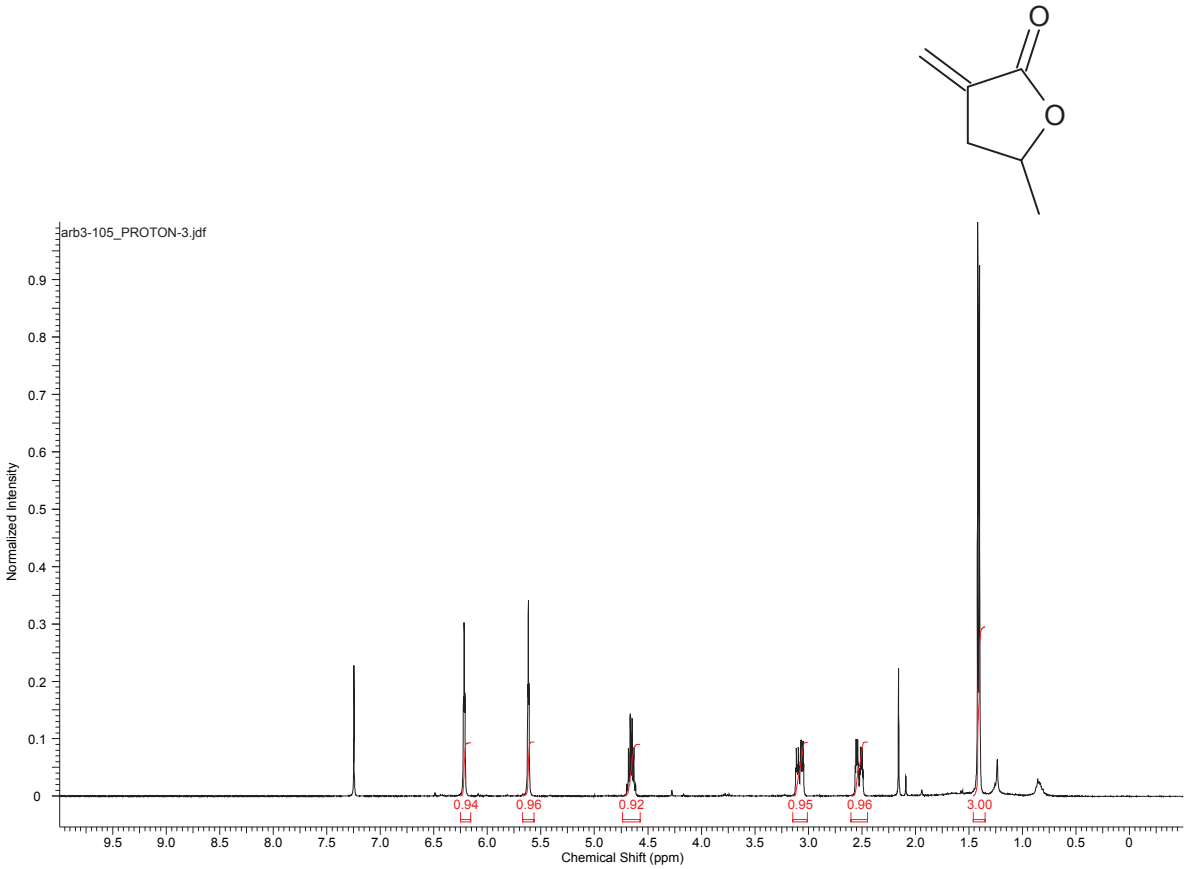


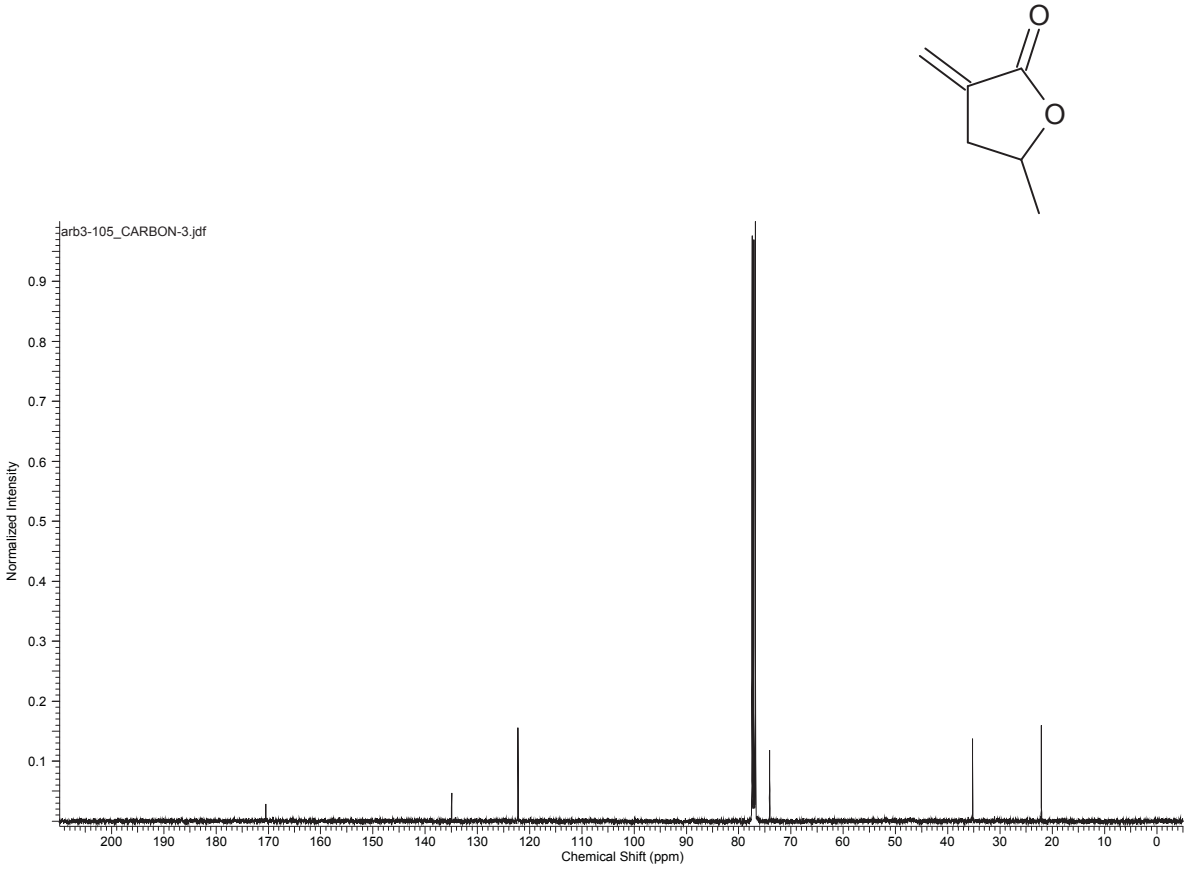


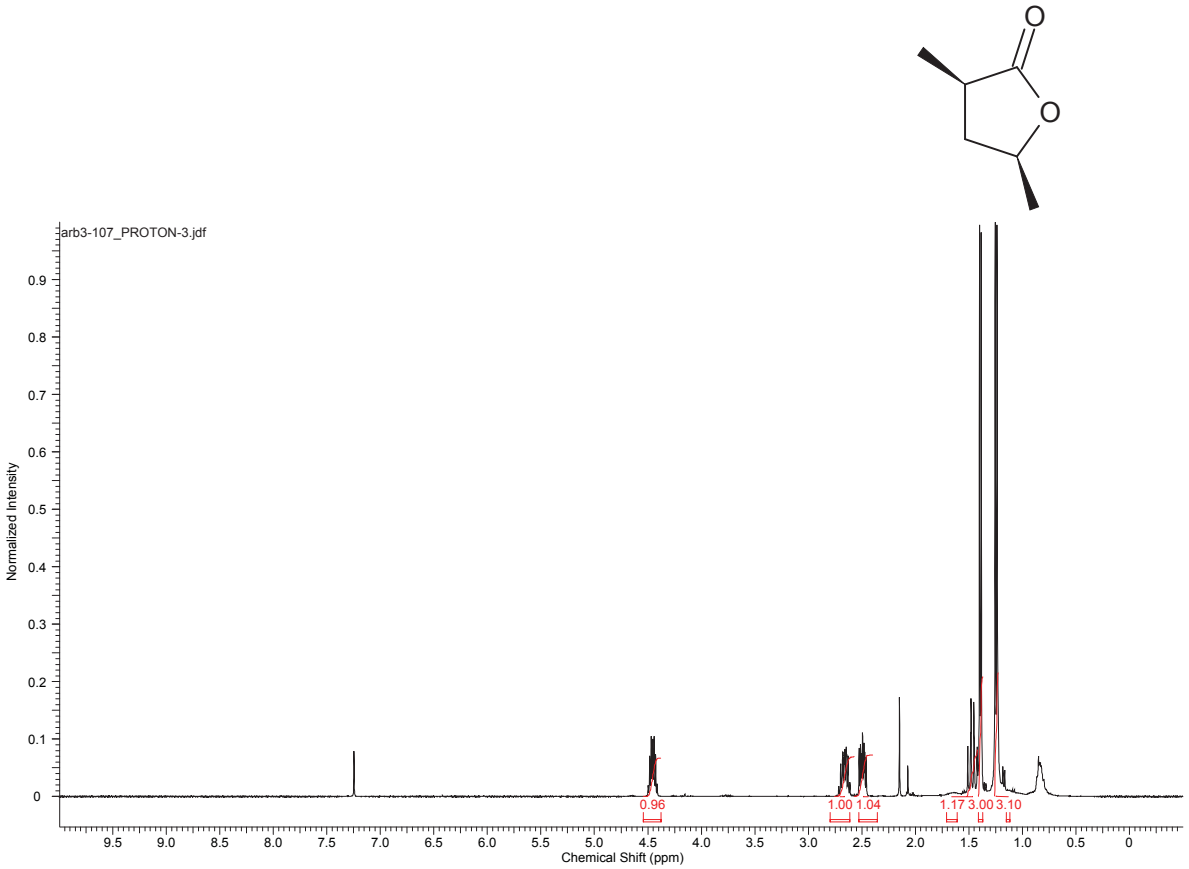


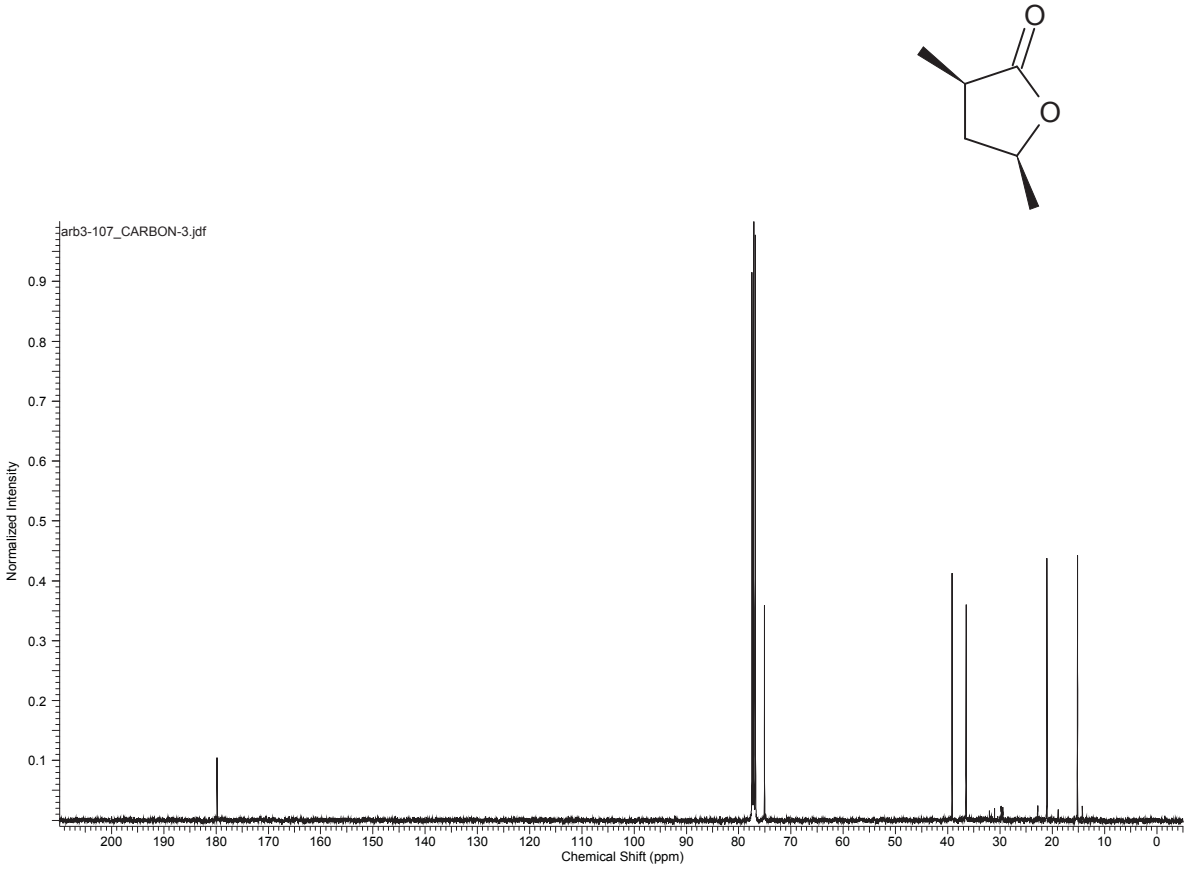










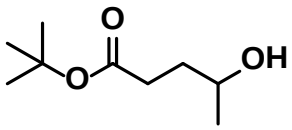


APPENDIX B

CHROMATOGRAMS

GC Chromatograms were obtained from an Agilent 7890A. The chiral column used was a Supelco Betadex 110. HPLC chromatograms were obtained from an Agilent 1260 infinity. The chiral column used was a Chiralcel OJ-H. Flow rates and times can be found with chromatograms.

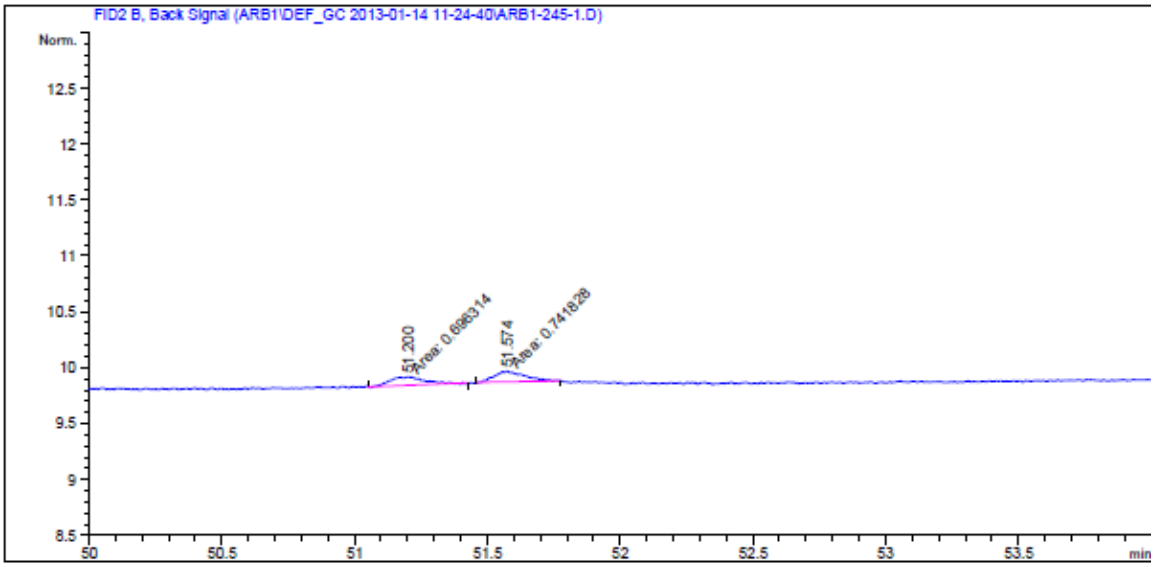
Substrate 99a



***99a*$_{anti}$**

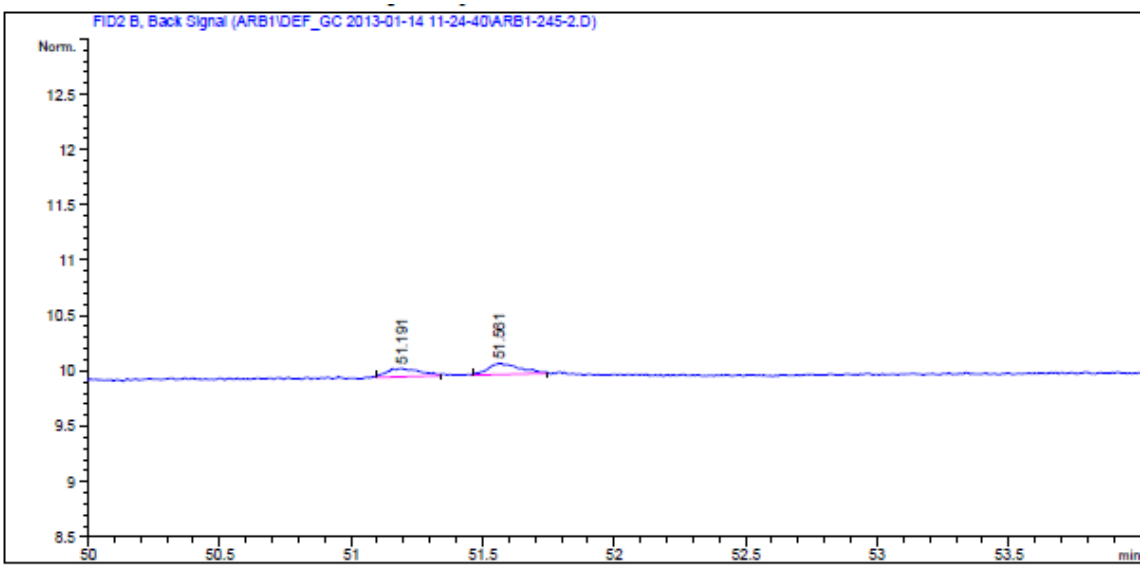
GC Conditions: Column: 190916-13213, 30m x 320 µm x 0.25 µm; Eluent Rate: 3 mL/min; Temperature Ramp: 50 ˚C for 30 min, ramp 2 ˚C/min → 170 ˚C, 170 ˚C for 10 min

Racemic



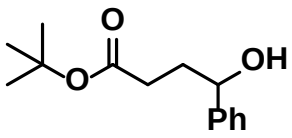
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	51.200	1	MM	6.96314e-1	7.63180e-2	48.41759
2	51.574	1	MM	7.41828e-1	9.34255e-2	51.58241

Enantiomeric



Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	51.191	1	BB	6.62918e-1	7.80856e-2	44.14106
2	51.561	1	BB	8.38900e-1	1.00154e-1	55.85894

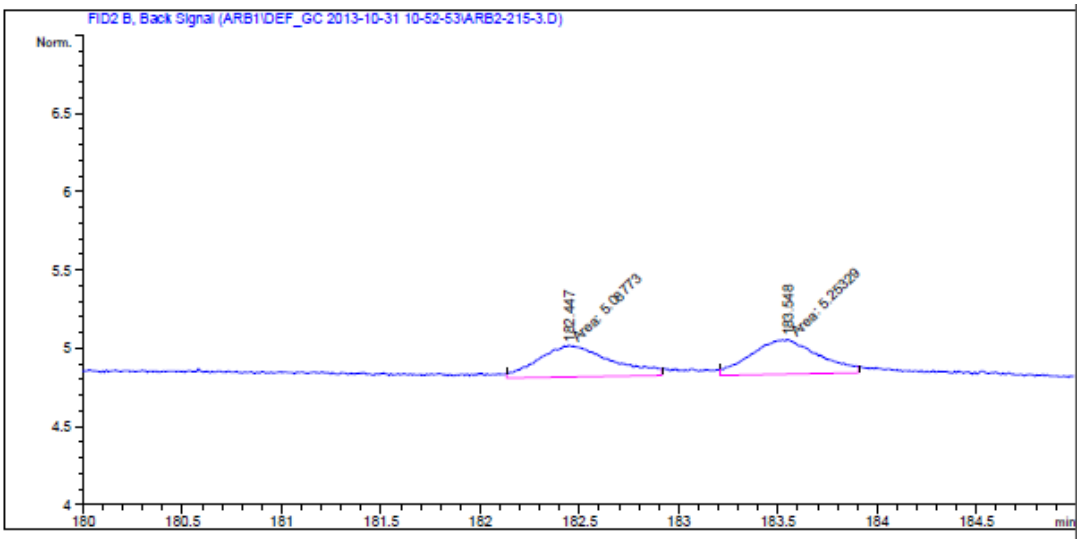
Substrate 99b



***99b*$_{anti}$**

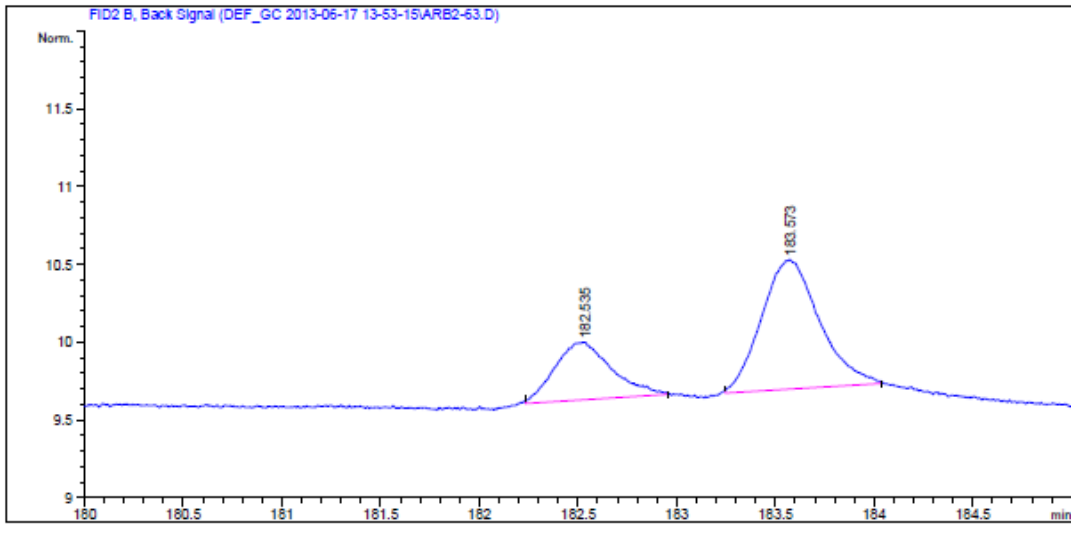
GC Conditions: Acetal derivative where H is replaced with Ac; Column: 190916-13213, 30m x 320 µm x 0.25 µm; Eluent Rate: 3 mL/min; Temperature Ramp: 100 ˚C for 60 min, ramp 2 ˚C/min → 120 ˚C, 120 ˚C for 60 min, ramp 2 ˚C/min → 140 ˚C, 140 ˚C for 60 min, ramp 2 ˚C/min → 170 ˚C, 170 ˚C for 60 min

Racemic



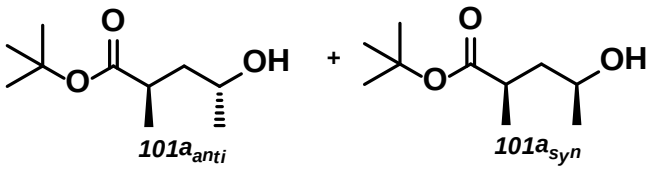
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	182.447	1	MM	5.08773	2.01564e-1	49.19947
2	183.548	1	MM	5.25329	2.20840e-1	50.80053

Enantiomeric



Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	182.535	1	BB	7.45226	3.70780e-1	30.51982
2	183.573	1	BB	16.96551	8.32658e-1	69.48018

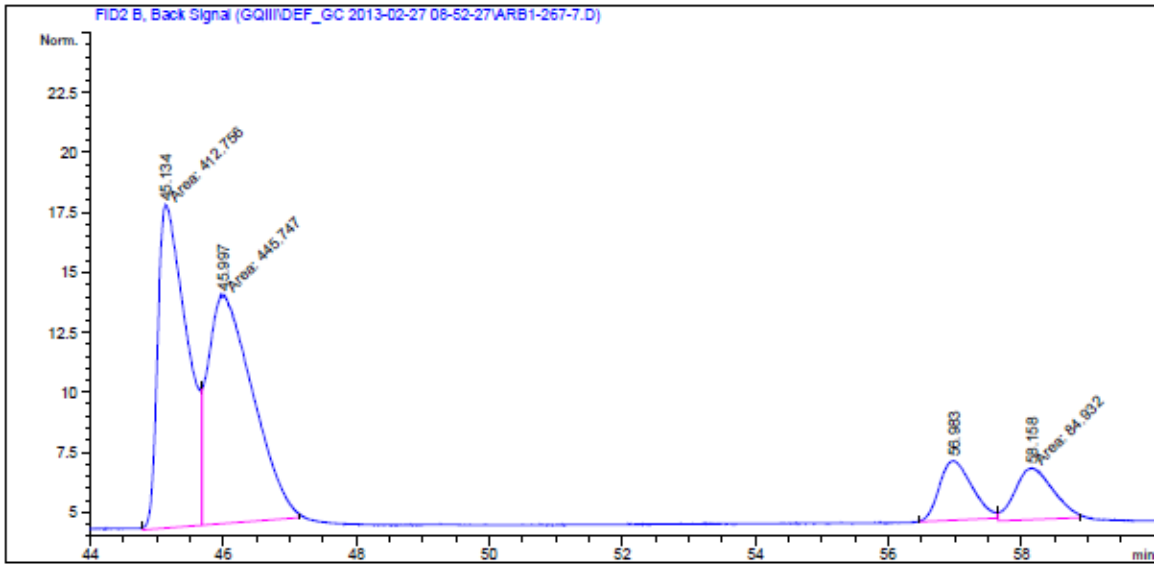
Substrate 101a



***101a*$_{anti}$** ***101a*$_{syn}$**

GC Conditions: Column: 190916-13213, 30m x 320 µm x 0.25 µm; Eluent Rate: 3 mL/min; Temperature Ramp: 70 ˚C for 60 min, ramp 5 ˚C/min → 170 ˚C, 170 ˚C for 10 min

Racemic



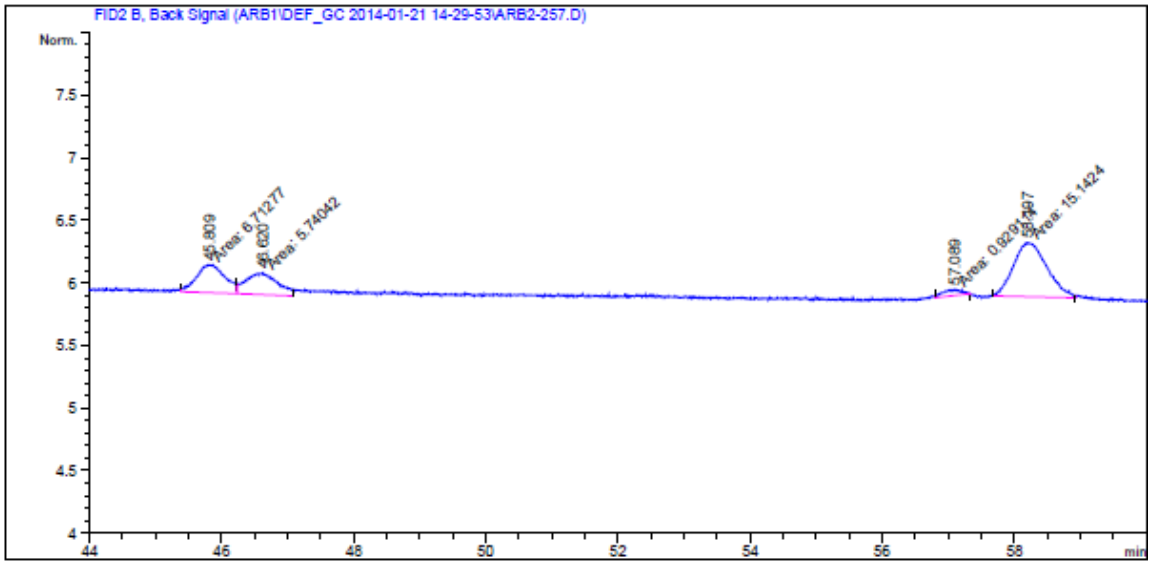
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	45.134	1	MF	412.75577	13.48362	40.14753
2	45.997	1	FM	445.74731	9.54117	43.35652

101a*$_{anti}$*

Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
3	56.983	1	BV	84.66241	2.48602	8.23486
4	58.158	1	MM	84.93200	2.14380	8.26108

101a*$_{syn}$*

Enantiomeric



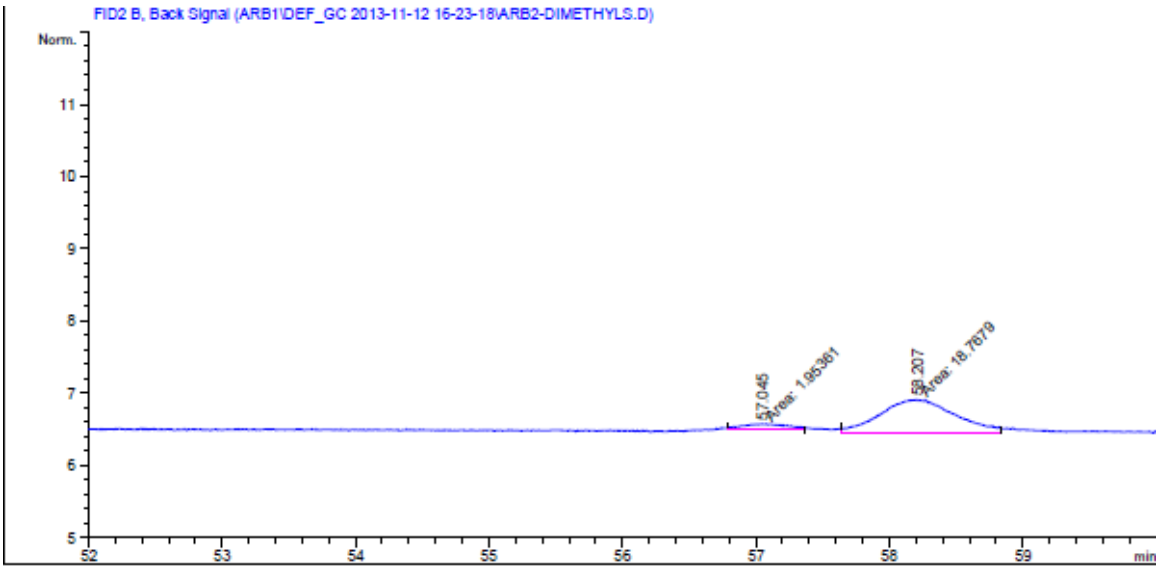
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	45.809	1	MF	6.71277	2.24447e-1	23.53322
2	46.620	1	FM	5.74042	1.70713e-1	20.12440

101a$_{anti}$

Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
3	57.089	1	MM	9.29114e-1	5.07450e-2	3.25723
4	58.197	1	MM	15.14236	4.35121e-1	53.08515

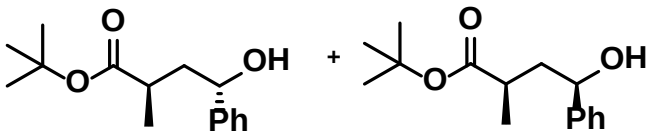
101a$_{syn}$

Large Scale Chromatogram



Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	57.045	1	MM	1.95361	8.14521e-2	9.42791
2	58.207	1	MM	18.76790	4.70131e-1	90.57209

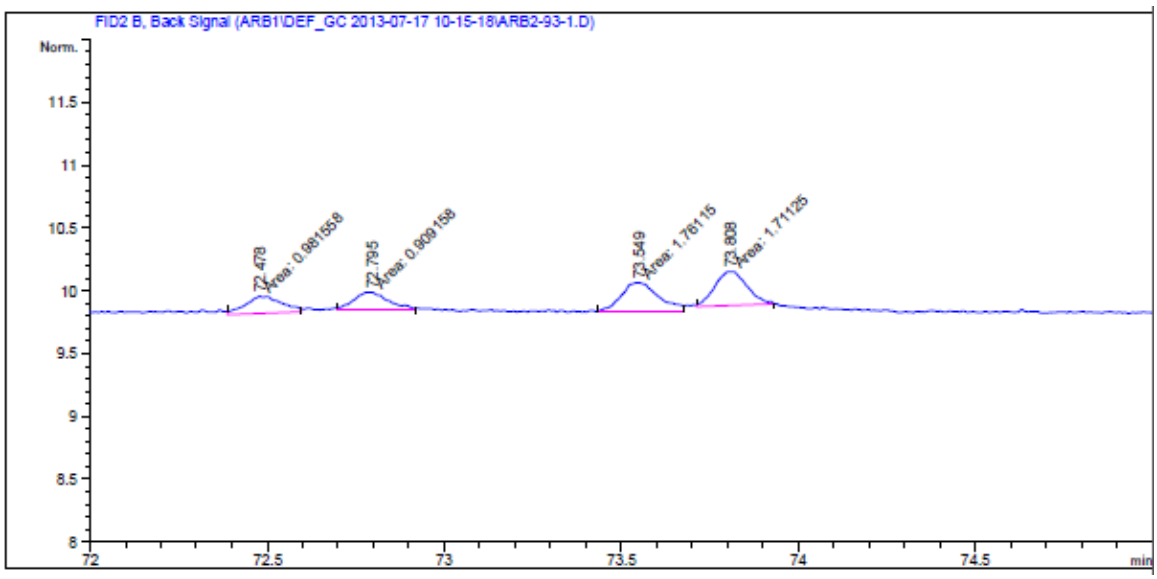
Substrate 101b



***101b*$_{anti}$** ***101b*$_{syn}$**

GC Conditions: Column: 190916-13213, 30m x 320 μm x 0.25 μm; Eluent Rate: 3 mL/min; Temperature Ramp: 120 ˚C for 60 min, ramp 5 ˚C/min → 170 ˚C, 170 ˚C for 60 min

Racemic



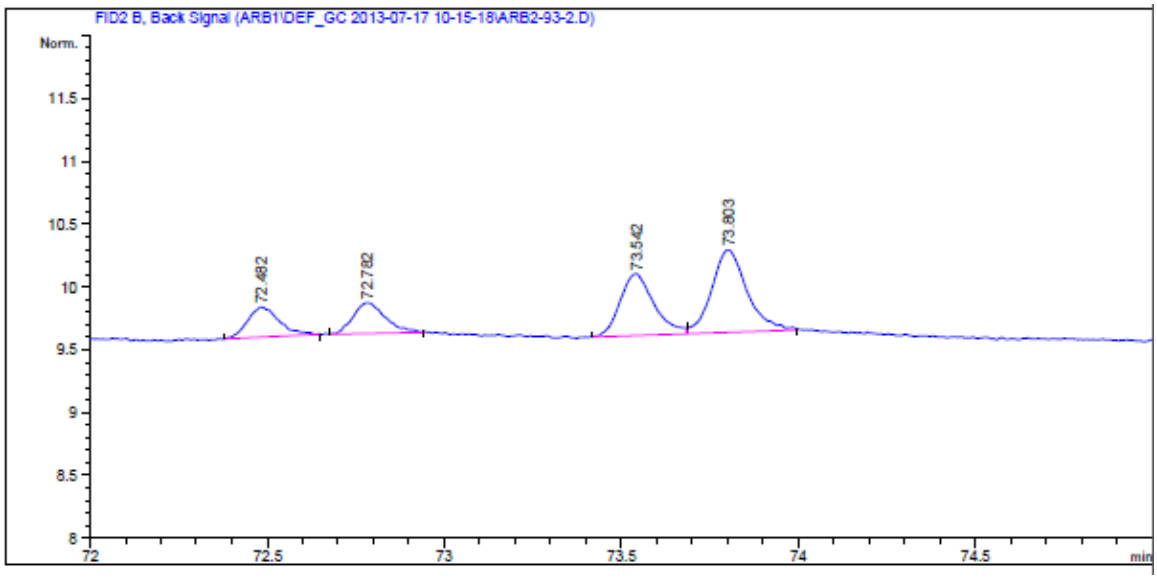
101b$_{anti}$

Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	72.478	1	MM	9.81558e-1	1.36514e-1	18.30204
2	72.795	1	MM	9.09158e-1	1.38644e-1	16.95207

101b$_{anti}$

Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
3	73.549	1	MM	1.76115	2.34483e-1	32.83816
4	73.808	1	MM	1.71125	2.70001e-1	31.90773

Enantiomeric



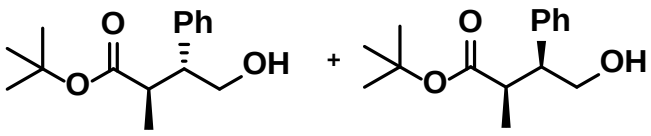
Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
1	72.482	1	BB	1.47951	2.38184e-1	13.68481
2	72.782	1	BB	1.54500	2.43365e-1	14.29059

101b$_{anti}$

Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
3	73.542	1	BV	3.24664	4.89890e-1	30.03000
4	73.803	1	VB	4.54017	6.58327e-1	41.99459

101b$_{syn}$

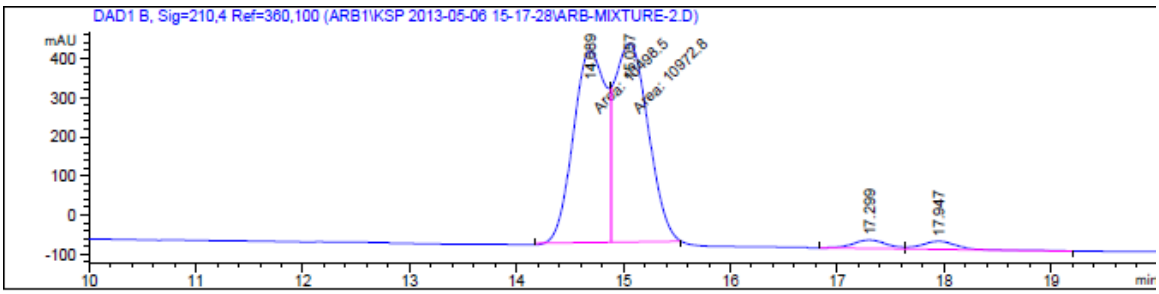
Substrate 100a



101b$_{anti}$ ***101b$_{syn}$***

HPLC Conditions: Column: OJ-H, 30m x 320 µm x 0.25 µm; Eluent Rate: 1 mL/min; Eluent Percentage: 5 % Isopropyl Alcohol, 95% Hexanes; Time: 30 min

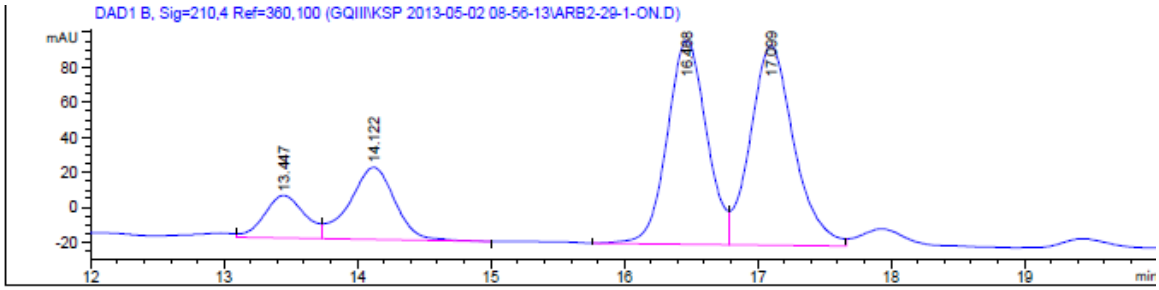
Racemic



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	14.689	2	MF	1.04985e4	490.22000	46.8623
2	15.057	2	FM	1.09728e4	508.21146	48.9791
3	17.299	2	BV	461.79837	21.42465	2.0613
4	17.947	2	VB	471.85135	20.36128	2.1062

100a$_{anti}$ **–** 1&2, **100a**$_{syn}$ **–** 3&4

Enantiomeric



Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	13.447	2	VV	509.44043	24.16732	7.9069
2	14.122	2	VB	972.88989	41.07418	15.1000
3	16.468	2	BV	2376.51807	116.22417	36.8854
4	17.099	2	VV	2586.13501	113.71803	40.1388

100a$_{anti}$ **–** 1&2, **100a**$_{syn}$ **–** 3&4